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RESERPINE AND OTHER TRANQUILIZERS: A REVIEW*

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I. INTRODUCTION

This review is dedicated primarily to our friends among the physicians and medical students who are currently drowning in a sea of tranquilizer brochures and samples. The current (1957) Physicians' Desk Reference lists more than 200 therapeutically indicated preparations under the title "anxiety and apprehensive states" and as large a list under "psychoses." Many of these are shotgun vitamin mixtures, some are steroids. Analeptics as well as barbiturate sedatives, alone and in combination, are represented. However, some of them contain agents which are relatively new, at least a few of which are so novel in their actions that they have excited the interest of many cinical investigators and laboratory scientists.

One result is that a new field of study has grown up in a very few years—the field of "psychopharmacology"—which borders on many disciplines and concerns itself with the mechanism of action of agents which are capable of changing behavior. The principal classes of new drugs which fall into the domain of psychopharmacology are the "psychotomimetics" which cause transient disturbances of behavior in man and laboratory animals, and the "tranquilizers" which prevent or mollify certain disturbances of behavior.

In the present review we will have little to say about the psychotomimetics except insofar as they have served as useful tools in the experimental study of behavior. It is, of course, the tranquilizers which most concern the clinician, and of these we will have most to say about the few subgroups which have proved relatively effective in the treatment of the most severely disturbed psychotic patients.

II. METHODOLOGY IN THE SEARCH FOR TRANQUILIZING DRUGS

A. Laboratory investigations: It might be of interest to survey the types of tests which are utilized in the laboratory to screen potential tranquilizers. First of all, it may be said that there is very little agreement among various laboratories as to which methods are most likely to give the most definite prediction of clinical value in advance of clinical trial[14]. Therefore a multiplicity of techniques for tranquilizer testing can be found in the literature[33, 41]. These methods defy classification, but can be crudely grouped as follows:

*The literature in this field is so extensive and so rapidly growing that it would be impossible to give adequate citation in a review of this length. However, it is hoped that two valuable sources will be available to the reader in the near future. One is an exhaustive and critical review by Wikler[40], the other a symposium volume edited by Gerard and Cole[41]. Meanwhile the interested reader will find his most compact sources in a series of symposium issues of the Annals of the N. Y. Academy of Sciences under appropriate titles, from 1954 through the present year.

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(1) Behavioral observations in normal animals: The untrained Rhesus monkey is a notoriously unpleasant laboratory species, given to outbursts of aggressive behavior and a generally ungrateful disposition. The ability of new drugs to make such animals more sociable to man, or at least more docile, has been used in a number of laboratories as a test for tranquilizing action.[15, 25] The most desirable drugs are those which produce docility without such untoward signs as ataxia, anorexia, weakness, loss of any of the normal motor and sensory repertoire, or any other signs than the desired limitations upon affective behavior. Other species have also been used.

In addition, observations on normal animals often give more special clues to the type of action. As an example, reserpine-like agents given in relatively large doses to mice produce a syndrome unlike that of any other class of depressants, with such features as a hunched and immobile posture, ptosis, and transient piloerection. Thus it is often possible to characterize a new agent as potentially tranquilizing by observation made in the earliest stage of drug screening[33].

(2.) Behavioral observations in animals with surgically-induced affective disturbances: As an example, certain strains of rats become violently aggressive after the placement of electrolytic lesions bilaterally in the septal nuclei by means of a stereotaxic instrument. The ability of drugs to normalize the disturbed behavior is considered a measure of potential tranquilizing value.

(3) Behavioral observations in drug-pretreated animals: A number of drugs are available for production of affective disturbances in various laboratory species. For example, cats are peculiarly prone to rage reactions after morphine. Some agents which have been claimed to be psychotomimetic in man are relatively weak in ability to produce corresponding changes in animals when given systemically. However, they may cause behavior disturbances when administered into the cerebral ventricles in animals, usually cats, which have been chronically prepared for this purpose.[12] The tranquilizers may give some degree of protection against the chemically-induced "psychosis."

(4) Behavioral observations in conditioned animals: This class of procedure is now demanding the attention of an increasing number of experimental psychologists.[3, 17, 18] Sometimes the techniques are most elaborate and the recording systems highly mechanized. Brady,[3] for example, first trains rats to press a lever in order to get water. When this training is established, an occasional shock to the feet is interposed and coupled with a neutral conditioning stimulus, visual or auditory. The normal animal eventually responds to the conditioned stimulus by ceasing his lever-pressing, and shows behavior that might be characterized as "anxious." The ability of a drug to circumvent the conditioned anxiety without impairing other features of behavior, including the condition ability of the animal for other tasks, is representative of tranquilizing action. Many simpler variants have been used.

(5) Other laboratory tests: A great number of tests have been described which have in common only the feature that they do not deal directly with affective behavior. A few may be mentioned. Many tranquilizers have the property of potentiating the sleep induced by a marginal dose of barbiturates. Some tranqilizers, particularly in the reserpine and chlorpromazine class, are able to prevent the normal elevation of electroshock seizure threshold which occurs in variously stressed animals.[33] Tranquilizers may reduce the ability of external stimuli to produce an alert type of EEG,[19,27,28] or to cause various reflex autonomic changes[29].

The few tests mentioned above illustrate a general property of tranquilizers which is of obvious clinical importance. These drugs, without necessarily impairing the higher functions of the nervous system, may reduce the affective repertoire as well as its autonomic correlates, or at least reduce the vulnerability of the animal to stress-induced changes. This is not an unmixed blessing, since it can be demonstrated that these normal changes often have survival value, and

that various stresses give a higher mortality in tranquilizer-treated animals[33].

B. Methodology in Clinical Investigations: [40, 41] The clinical trial period for many new tranquilizers has seemed indecently short, to the extent that the agent is often available over the counter long before the pertinent literature appears in print. However, these drugs are marketed only after approval, for use as labelled, by the Food and Drug Administration. F.D.A. approval implies only safety in the intended use, as determined by acute and chronic animal investigations, and by preliminary clinical investigational trials. Sometimes old wine appears in new bottles, and a previously approved antihistaminic may be marketed under a new name as a tranquilizer, having received a new-use permit with a minimum of new investigation. This is particularly unfortunate since a number of the "new-use" tranquilizers are nonprescription items, beyond the control of the physician. However, under present law the practice is valid. There is a growing conviction among many psychopharmacologists that all tranquilizers possess a "behavioral toxicity" potential in the hands of the ambulatory unrestricted patient. If so, a new law requiring that tranquilizers be sold only on prescription is sorely needed.

Clinical investigations of new tranquilizers have been characterized in general by wide variability of design and of results. In some instances, the testing institution employs rigorous double-blind procedures, matched test and control populations, elegant statistical evaluation. At the other extreme, the most desultory clinical impressions may become incorporated into the literature. As an example of careful design, one might mention the current testing program of the Veterans' Administration Hospitals, which unfortunately is restricted to two phenothiazine preparations. We should not like to infer, however, that institutional testing is superior to that in private practice. Psychiatrists in private practice have often contributed to the literature very important observations on side-effects, differential indications, and notes on physiological mechanisms.

It is important that these new pharmacological agents should be seen in a wide variety of applications before a final judgment is made on their clinical worth. Useful populations for clinical investigation have included, and should continue to include, such groups as: state institution agitated psychotic wards, with both chronic and acute samples; private hospital wards, which often yield small but valuable samples of acute cases in several categories; psychiatric out-patient clinics, including post-hospitalization follow-ups; general hospital and out-patient cases with obvious emotional components of their organic complaints; a variety of ambulatory patients seen in private practice; special institutional categories such as alcoholics and narcotics withdrawal cases; where possible, acute tests on normal human volunteers. Much of the discrepancy in the literature concerning effectiveness of different tranquilizers reflects the difference in the populations which were sampled.

One feature contributing to over-optimistic appraisals of new tranquilizers is the well-known therapeutic effect of any type of increased intervention in the lives of chronically institutionalized psychotics. The possibility is often apparent that an atmosphere of enthusiasm and hope can contribute as much as the administration of the test drug. But, notwithstanding these equivocal features of tranquilizer testing, one cannot help but be impressed by the sheer weight of manpower which has gone into the clinical investigation of these drugs. The extent of this participation is surely a reflection of the recognized importance of the problem of psychopathology in our society.

III. USES AND MODE OF ACTION OF TRANQUILIZERS

A. Rserpine and congeners (Rescinnamine, Deserpidine)

1. History: According to Kline,[20] the plant now known as Rauwolfia was mentioned in ancient Arabic and Greek medical writings. In 1582 the naturalist and physician Leonard Rauwolf returned to Europe from a trip to India with samples of this plant and information on its medical uses in the East. The plant re-

mained in continuous use in India and was also mentioned from time to time in Western pharmacognosy even up to the present century.

The modern period of scientific and medical interest in the plant **Rauwolfia serpentina** began in India in 1931 when Siddiqui and Siddiqui[32] isolated some active alkaloids. In India in the same year, the hypnotic actions of Rauwolfia preparations were studied by Ray,[26] and their value in psychiatric practice was reported by Sen and Bose[30]. Shortly thereafter Chopra et al.[7] published concerning the hypotensive actions of Rauwolfia, and by 1942 Bhatia[2] had amassed and reported considerable favorable clinical evidence with these preparations. However, it was not until 1949, when Vakil[35] published convincingly in the British Heart Journal, that western interest was finally aroused, leading to the confirmatory work of Wilkins[36, 37] in America in 1952. In this same year, Mueller et al.[22] isolated the active crystalline preparation now known as reserpine.

The psychiatric uses of Rauwofia continued to be reported in provincial Indian medical journals and disregarded elsewhere until Hakim[14], in 1953, received a prize in India for an outstanding critical review of this subject and was mentioned in the American press. Finally, in 1954, in this country, Kline[20] and independently Noce et al.[23] reported their confirmations of the value of reserpine in psychiatry.

2. Clinical uses and side-effects of reserpine: The literature on this subject is by now so extensive and well-known that it would be discriminatory to give any individual citations. Suffice it to say that in general the chief indications for the use of reserpine and its congeners are still hypertension and behavior disorders.

(a) As a *hypotensive*, reserpine is not comparable in effect with such agents as the veratrum preparations and the ganglionic blocking agents. However, its relative safety and prolonged action make it highly valuable particularly in ambulatory patients and in those patients whose hypertension is in part of psychogenic origin. It must be recognized that the dosages used in hypertension are usually on the low side (less than 1 mg./day), insufficient to achieve complete adrenergic blockade (see below). At any rate, clinical usage of reserpine in hypertension is ordinarily such as to make use of the minimal central actions of this drug to give the patient a degree of protection against the stresses which otherwise might maintain a labile hypertension.

(b) By far the most dramatic use of reserpine has been in the *treatment of mental illness, particularly in institutionalized schizophrenics.* A number of careful studies, such as those of Kline[20], illustrate the value of reserpine in restoring previously unmanageable patients to social usefulness.

There is somewhat less evidence for the usefulness of reserpine in psychotic states other than the schizophrenic. For example, psychotic depression is not necessarily allayed; to the contrary, suicidal depressions have been reported after many months of chronic usage of reserpine in patients under treatment for other reasons[13]. We still have no adequate pharmacotherapy for the psychotic depressed state.

Although widely used in the treatment of anxiety and of various disorders such as hypertension in which anxiety is thought to play a role, reserpine cannot be considered an euphoriant. For this reason the patient often prefers other available medications. Narcotic addicts, who are particularly attuned to the euphoriant element of new medications, offer an instructive example in this regard. In local experience[21] with deserpidine, a reserpine congener, in narcotics withdrawal, we have seen definite alleviation of physical signs and insomnia associated with the withdrawal, despite which the patients do not consider it to be adequately euphoriant medication.

Similarly, reserpine is not a sedative in the usual sense of the word. Patients may sleep better or more regularly in comparison with previous habit, but reserpine does not induce sleep in the man-

ner of barbiturates. Wakeful quiescence rather than drowsiness seems to be a more characteristic action. Insomnia or vivid dreaming are sometimes reported.

(c) **The time course of action** of reserpine must be taken into account. After a single dose by whatever route, the peak effect is not attained for several hours. The action is then sustained for days. Therefore, reserpine cannot be expected to give prompt amelioration of signs comparable to chlorpromazine, for example, in acutely disturbed psychotics. Because of the prolonged action, there is little reason for giving doses more frequently than once a day. In the chronic treatment of psychotics, it is notable both with reserpine and chlorpromazine that patients may go through a phase of "turbulence" lasting up to several weeks before the more stable phase of social adjustment sets in.

(d) **Side-effects** attending the use of reserpine and its congeners are many but usually not serious and often easy to overcome with supplementary medication. For example, *congestion of the nasal mucosa* is common but may be opposed by antihistaminics. *Gastrointestinal hyperactivity* may be covered by atropinic drugs. *Overtranquilization* may be opposed by centrally acting sympathomimetic amines of the general class of amphetamine.

Somewhat more serious in appearance are those neurological side-effects which suggest involvement of basal ganglia. These usually resemble clinical *Parkinsonism,* but include other types of pathological involuntary movement. Some experienced clinical investigators prefer to push the dosage if necessary to the point where Parkinsonism appears in order to achieve control in psychotic patients. Atropine and other anti-Parkinson agents may then be used as adjuncts.

Among the more serious but fortunately infrequent toxic effects are those attributable to loss of *temperature regulating mechanisms.* The patient may develop an unexplained high fever in association with a minor upper respiratory infection or perhaps none at all. The reserpinized patient loses some of his ability to regulate body temperature against extremes of both heat and cold, and particularly in large institutions with poor surveillance and no air-conditioning this kind of catastrophe may be recognized too late.

Another possible serious outcome may result in patients undergoing electroshock, where reserpine may intensify the seizure and deepen the post-ictal depression. This is also a problem in clinical epilepsy, where indiscriminate use of reserpine should be discouraged. In spite of occasional favorable reports, *reserpine is not an anticonvulsant.* A small but significant percentage of nonepileptics develop seizures under reserpine treatment. Fortunately the use of anticonvulsant medication does not appear to interfere with the other actions of reserpine.

Other occasional serious side-effects include occasional *acute hypotensive crises,* perforation of *peptic ulcer,* and severe *epistaxis.* None of these considerations is peculiar to reserpine alone since almost the same spectrum of toxicity may be seen with chlorpromazine and with other phenothiazines, despite differences in mechanisms of action.

3. The **daily dosage** range of reserpine is wide, favorable reports having been published in various conditions with doses of as little as 0.1 mg and as much as 6 mg/day. Because of slow onset and good absorption, oral preparations are usually satisfactory.

4. **Other preparations** include a number which contain reserpine in combination with various hypotensives, sedatives, central stimulants, etc. It should be remembered that the reserpine effects ordinarily long outlast those of the medications with which reserpine is usually combined.

There are also a number of available preparations containing one or more Rauwolfia extracts in addition to reserpine. Another available pure alkaloid of Rauwolfia is *rescinnamine,* which differs from reserpine in being the cinnamic rather than the trimethoxybenzoic ester. *Recanescin,* also reported in the literature as *desmethoxyreserpine* and

deserpidine, differs from reserpine only in the absence of one methoxy group. The minor chemical differences between these three molecules confer quantitative but not qualitative differences in action. Therefore, without detailing the relative advantages, it may be sufficient to say that indications and contraindications are similar and dosage is of the same order.

5. Mechanism of action of reserpine

(a) **Characteristic effects in animals:**

A very extensive literature already exists on animal studies concerned with reserpine action, of which the review of Plummer et al.[25] is representative. Most of these studies can be disposed of by saying that they demonstrate autonomic and behavorial effects which are by now known also for man. Tremor, hypothermia, hypotension, etc., are all evident in various species. Considerable effort has gone into the designing of conditioned reflex experiments to reproduce some of the subtlety of these drug effects on human behavior. Of these, the experiments of Brady[3] are typical in demonstrating that reserpinized rats may overcome a conditioned emotional response which interferes with a conditioned lever-pressing response required to obtain water. Thus reserpine in animals as in man appears to be capable of reducing affective responses without more generalized loss of conditioned repertoire.

Other experiments are concerned with localizing the site of reserpine action in the brain by stimulation and recording from various sites[19, 28]. In general, these studies have tended to restrict the locus of reserpine action to such sites as medulla and hypothalamus. Respiratory and autonomic responses normally carried out through the medulla are in general impaired in such a manner that the site of blockade appears to be afferent to the particular integrating center. The behavorial effects cannot be explained as a suppression of the currently popular diffuse ascending reticular activating system, since EEG studies indicate that activation is prominent in the resting animal.

In our own work[33], we have been concerned with the thesis that reserpine operates by reducing certain inhibitory mechanisms essential to the adequate performance of a number of physiological regulations, including postural, thermal, cardiovascular and affective. This view was based on the finding that reserpine and such active congeners as deserpidine reduce the initial inhibitory phase of induced seizures, and further prevent the inhibitory action of certain types of stress upon seizures. An anti-inhibitory action of reserpine can be shown even in decerebrate animals. The reserpine effect can be overcome by only a few agents, chiefly sympathomimetic amines (but not by serotonin).

It is now certain that reserpine and its active congeners produce most if not all of their effects by intervention in the mechanism of formation and release of some physiologically active amines. In particular the loss of adrenalin and noradrenalin from the body are of prime importance. The loss of serotonin also occurs but the role of serotonin in the body economy is more controversial. The present status of the concept of serotonin (5-hydroxytryptamine, Erspamer's "enteramine") as a chemical mediator in the central nervous system is reviewed in a series of symposium articles by Page[24], Udenfriend[34], Shore[31], Wooley[39] and several other contributors. Since in our own experience the actions of serotonin on central nervous function are much less dramatic than those of adrenalin or noradrenalin, we would prefer to discuss the latter in more detail.

Carlson and Hillarp[6] and later Holzbauer and Vogt[16] made the very important observation that reserpine produced a long-lasting and severe deficit of catecholamines. This appears to be true both of noradrenalin and adrenalin whether in the adrenal medulla, in sympathetic ganglion cells, or in brain. Shore et al.[31] have confirmed these observations for the most part, with some remaining question about the resistance of the adrenal medulla to lysis by reserpine. Recently it has been shown[5] that human blood levels of noradrenalin are markedly reduced by reserpine, the recovery period requiring many days.

Adrenalin levels were more questionably affected.

Thus chemical determinations have demonstrated that reserpine produces a definite and prolonged suppression of the noradrenalin mechanism and possibly but less clearly of adrenalin. This finding alone could account for most of the observed peripheral actions of reserpine. Whether it explains the central effects is less sure. Although cells containing noradrenalin are scattered throughout that part of the brain close to the midline of the floor of the ventricular system, their function is still undetermined. Adrenalin and noradrenalin have never been notable for their central effects, at least in any reasonable dosage. The possibility that other still undiscovered amines may be involved should not be excluded.

Some of the above considerations are illustrated in the following paragraphs by a series of experiments reported by Everett et al.[9]. We have worked primarily with deserpidine rather than reserpine, but a few parallel experiments indicate that there are no qualitative differences between the two drugs. The experiments are offered as a pharmacological proof of site of action.

Within less than an hour after administration of deserpidine or reserpine to mice or rats, the body hair fluffs up in a typical piloerection response such as may be obtained in normal animals by placing them on ice. The pilomotor muscles are well known to be contracted by adrenergic agents, and have often served as bioassay objects for circulating adrenalin, etc. As might be expected, the transient piloerection produced by deserpidine can be blocked by dibenamine, which is known to abolish the response of many types of effectors normally excited by adrenergic mediators. Therefore deserpidine cannot be acting directly on the effector. The transient piloerection is not blocked by such ganglionic blocking agents as inversine. Therefore the deserpidine must be acting directly on post-ganglionic sympathetic cells to cause a release of the mediators. Sympathetic nerves removed from the animal during this stage do not show spontaneous action potentials nor any other significant change. Therefore deserpidine must cause release of adrenergic mediators without the intervention of nerve impulses. Normally it is the occurrence of nerve impulses in the sympathetic fibers which presumably causes the release of mediators. In short, deserpidine acts directly upon some precursor system to release adrenergic mediators.

After an hour or so following deserpidine or reserpine treatment, the initial piloerection is gone and the full picture of reserpinization is evident. Behaviorally, the animals show a hunched and immobile posture, squinting, etc., but are not asleep—they are "tranquilized." Body temperature is lowered. Various signs of sympathetic inadequacy may be studied. Of these the most evident is paralysis of the pilomotor apparatus. The fully reserpinized rodents show no piloerection when placed on ice. Ganglionic stimulants such as carbachol, which normally cause piloerection, no longer do so. Only adrenalin and noradrenalin are capable of causing a maximal piloerection. Serotonin and such adrenergic stimulants as desoxyephedrine do not evoke an adequate piloerection. Therefore the picture is that of a primary deficit in both adrenalin and noradrenalin.

If one removes sympathetic nerves from such animals, they behave normally in the nerve chamber with regard to excitability and action potential. Therefore there is no deficit in impulse conduction, but only in the availability of meditator for release.

This deficit of adrenergic mediator persists in rodents for a week. The central nervous changes persist a corresponding time. Is it possible to account for these central changes solely on the basis of an adrenergic deficit? Not quite, for the following reasons: Adrenalin or noradrenalin given to the fully reserpinized animal may reverse some signs, such as the squint, but do not fully restore normal posture and exploratory behavior. Desoxyephedrine is much more affective in this regard, but is not a complete antidote. Serotonin, incidentally, is quite ineffective. Iproniazid, an amine oxidase

inhibitor which would presumably prolong and therefore increase the action of residual amines, gives some poor reversal. Therefore, although one can account for certain peripheral signs of reserpine action on the basis of deficit of adrenergic mediators, the central signs are not completely accountable on this basis.

One is led to wonder whether some other amines, more related to adrenalin than to serotonin, may not yet be found in the central nervous system.

On the basis of these and a number of other observations, our own present concept of reserpine action on the central nervous system is somewhat as follows:

There are a number of sites in the brain, from medulla to basal ganglia, which are embryologically derived from the same cell columns which in the spinal cord give rise to emigrant adrenergic ganglion cells. The non-migrant brain cells of adrenergic type act, by means of mediators still unknown, upon effectors—the glia and endothelial cells—which in turn modulate the immediate environment and excitability of neurones within the centers. Through this indirect non-neural link various protopathic afferent and other systems are capable of modifying synaptic transmission in a number of ongoing reflex regulations, in such a manner as to make the regulations more appropriate for coping with various emergencies. Under the influence of reserpine this adrenergic link is blocked. In contrast, certain behavioral disorders are characterized by excessive and continuous function of this adrenergic link. Reserpine diminishes the continuous hyperfunction, but unfortunately also impairs a number of important regulating functions. This is the price of tranquility.

B. Chlorpromazine and Other Phenothiazines

If this were a systematic review, chlorpromazine would deserve a much space as reserpine on the basis of its even more widespread use, its similar indications and efficacy, and its equally interesting pharmacology. Indeed it was with this agent rather than reserpine tnat the new era of pharmacotherapy of psychoses was ushered in[8]. However, it is convenient for our present purpose to restrict attention mostly to those features of chlorpromazine which differentiate it from reserpine.

Unlike reserpine, chlorpromazine is a synthetic molecule. Chemically it is 10-(gamma-dimethylaminopropyl)-2-chlorophenothiazine. It is closely related to the antihistaminic phenergan, although in itself not a potent antihistaminic, and also to the anti-Parkinson agent diethazine, although chlorpromazine in itself may cause side-effects resembling Parkinsonism. Thus it is evident that small changes in the molecule of this drug group may produce qualitative differences in action. A number of new phenothiazine derivatives closely related to chlorpromazine are now available and will be mentioned separately.

1. Clinical Indications and Side-Effects of Chlorpromazine

A considerable literature attests to the usefulness of chlorpromazine in the psychoses, particularly in *schizophrenia.* The psychiatric indications appear to be in all major respects the same as those for reserpine. However, chlorpromazine is much more rapid in its onset of action and is capable of inducing a more profound depression of the central nervous system. Therefore it is more useful than reserpine for the prompt management of *acutely disturbed patients.*

Chlorpromazine is not as lasting in its action as reserpine, and therefore divided doses are probably preferable. The latitude in *dosage range* is wide for treatment of psychoses, and one can find favorable reports in the literature with as little as 50 mg./day and as much as 400 mg./day. The level of 200 mg./day is frequently used in institutional practice.

As with reserpine, the over-all time-course of chronic therapy with chlorpromazine is often marked by a *turbulent phase* of several weeks before social remission becomes stable. Likewise *depressive symptoms* have sometimes been manifest after prolonged therapy, possibly less than with reserpine. Chlorpromazine is clearly not an antidepressive.

Like reserpine, its chief differential indications are therefore in *schizophrenia* and *agitated manic* or *hypomanic states.*

Like reserpine, chlorpromazine also has *hypotensive properties,* but has not been as widely used in this application.

Several useful actions of chlorpromazine are not shared by reserpine. For example, chlorpromazine is one of the most effective *antiemetics* now available and is active in almost all disorders characterized by vomiting with the notable exception of motion sickness. *Intractable hiccough* and some types of *chronic cough* may also be managed. These results are probably related to a direct action of chlorpromazine on medullary centers whicr are not affected by reserpine.

Chlorpromazine has been used, particularly abroad, to aid in reducing body temperature in preparation for surgery under *refrigeration anesthesia.* One might expect reserpine to be just as effective if the action was restricted only to the hypothalamic thermal centers, but the peripheral autonomic mechanisms of chlorpromazine are different and more diffuse, as will be seen later.

Many *side-effects* of chlorpromazine are similar to those of reserpine. These include the *Parkinson-like* syndrome, *reduced temperature regulation, lethargy, hypotension,* and increased vulnerability *to seizures.*

Some side-effects much more frequently seen with chlorpromazine than with reserpine include *hypermastia* and *lactation,* even in preadolescents. *Menstrual disturbances* are also frequently described. An action through the hypothalamus upon the anterior pituitary is therefore not unlikely.

A few side-effects of chlorpromazine are notably absent with reserpine. These include *jaundice,* a *dermatitis* which is sometimes photosensitive, and rarely, *agranulocytosis.*

2. Mechanism of Action of Chlorpromazine

From the similarity of effects of reserpine and chlorpromazine, one might expect a similarity in basic mechanism of action. This is not the case. Chlorpromazine has been reported to have mild blocking effects on a wide variety of peripheral effectors, opposing the actions of acetylcholine, histamine, and particularly adrenalin, but these actions are at best partial and inconsistent, and do not explain the more profound depressant effects of chlorpromazine on various autonomic reflexes and regulations. These actions are exerted predominantly on the central nervous system itself. Centers involved include those for various cardiovascular, respiratory and vomiting reflexes in the medulla, as well as the thermoregulatory centers of the hypothalamus.

The central mechanism of action of chlorpromazine is moot[19]. Many authors have reported the appearance of slow activity in the EEG with chlorpromazine, with greater difficulty in producing an arousal pattern by sensory stimulation or by direct stimulation of the mesencephalic reticular activating system. However, the EEG changes do not appear to be proportionate to the behavioral changes in animals and they may even disappear at higher doses which affect behavior more profoundly. They are not a notable feature of the human EEG. At any rate, the situation is different from that observed under barbiturates where the EEG changes are greater in kind than the deficit in arousability, and certainly different from the reserpine effect, where tranquilization is often associated with a more alert type of EEG. There is obviously a serious discrepancy between behavorial arousal and so called EEG arousal. The most striking example of this discrepancy is the action of atropine, which causes a slow EEG but increases behavorial alertness. The relevance of this dissociation for the present discussion is that it is not necessary to equate tranquilization with depression of the mesencephalic activating system.

There is some evidence for an action of chlorpromazine on cerebral structures known to be concerned with affect, including the amygdaloid and hippocampus. However, there is no reason at present to demand that chlorpromazines or any other tranquilizer should act only on a single brain structure.

In general, the central zone of action of chlorpromazine seems broader than that of reserpine, and the maximum behavioral and neurological impairment which can be obtained is consequently greater. If one follows the analogy in peripheral action, it would be expected that chlorpromazine would act upon central non-neural effectors which normally respond to mediators analogous to histamine, acetylcholine and adrenalin, especially the latter. In contrast, reserpine action is limited to the production of a deficit in adrenergic transmission. The end result might well be qualitatively similar, since with both drugs regulatory circuits involving adrenergic mediation would be impaired. Thus, despite differences in basic mechanism of action, the common features of therapeutic efficacy and side-effects of reserpine and chlorpromazine would be explained.

3. Promazine

Recently the search for phenothiazines lacking in the somatic side-effects of chlorpromazine (especially jaundice) has led to the introduction of several new agents. Promazine is simply chlorpromazine minus the chlorine atom. The result appears to be that promazine is about half as potent and half as toxic, so that, for example, 400 mg./day would be an appropriate dose level corresponding to 200 mg./day of chlorpromazine. At present the two agents are undergoing an extensive comparison in Veterans' Administration hospitals.

4. Other Phenothiazines

The present trend toward new phenothiazines is in favor of more potent compounds. This effect is being attained in a number of instances by incorporation of the amine nitrogen in a ring structure. While the somatic effects may be avoided, the potency seems to inclease also for such central toxic signs as Parkinsonism and seizure vulnerability. Two such preparations, *prochlorperazine* and *perphenozine* are respectfully about five and ten times as potent as chlorpromazine.

C. Meprobamate

Prior to the present wave of tranquilizers, there had been scattering reports of anxiety-reducing properties of various agents used for other purposes. Among these was mephenesin, the centrally acting muscle relaxant. Since mephenesin was not dependable as a chronic oral medication for its intended use, largely because of its rapid metabolic destruction, considerable research was directed toward longer-acting substances, among the glycerol ethers and related structures. Out of such investigations by Berger and his colleagues came meprobamate[15]. Originally considered as a muscle relaxant and also as a possible anti-petitmal agent because of its relation to prenderol, it is now the most widely used tranquilizer.

1. Clinical uses and side-effects of meprobamate

Meprobamate is 2-methyl-2-n-propyl-1, 3-propanediol dicarbamate. *Dosages* required are in the region of 2 grams per day. Although it has been reported as effective in populations of institutionalized psychotics, the preferred and widest usage is for management of *anxiety* in all of its forms in the ambulatory population. In comparison with the tranquilizers of reserpine and chlorpromazine type, it is certainly more *euphoriant*, and at least mildly *sedative*.

Because of its ability to ameliorate *muscle spasm* and *tension* of various kinds, it seems more dependable than mephenesin in chronic oral medication of these conditions. It also appears to be effective in the treatment of *petit mal*, but not of major seizures.

The *side-effects* are usually dose-related and of *central origin*, in general not unlike those to be expected from such central depressants as ethyl alcohol and barbiturates,—and as variable. The latitude in dosage, however, seems rather large. There is still some question as to whether tolerance, dependence, addiction liability and withdrawal excitement or even convulsions may occur. These are of course dangers which are to be considered in any central depressant which has euphoriant properties. *Somatic side-effects* seem rather rare and idiosyncratic. *Purpura* has been reported.

Table 1

SUMMARY OF PRINCIPAL TYPES OF TRANQUILIZERS

Official and alternative generic names in italics, with some common trade names in quotations. Drug combinations are not included.

RESERPINOID: Probably acting primarily by causing prolonged deficit of adrenalin, noradrenalin and possibly serotonin.

Reserpine: "Serpasil," "Serpiloid," "Sandril," "Serfin," "Reserpoid,' "Serpate," "Rau-Sed."
Rescinnamine: "Moderil."
Recanescin, deserpidine, desmethoxyreserpine: "Raunormine," "Harmonyl."

PHENOTHIAZINE: Diffuse partial autonomic blockade, especially adrenergic.

Chlorpromazine: "Thorazine," "Largactil."
Promazine: "Sparine."
Prochlorperazine: "Compazine."
Perphenazine: "Trilafon."
Pecazine, mepazine: "Pacatal" (see also below).

ANTICHOLINERGIC: Predominantly atropinic actions.

Pecazine, mepazine: "Pacatal" (see also above).
Benactyzine: "Benzityl," "Suavityl."

ANTIHISTAMINIC:

Chlorcyclizine: "Perazil."
Diphenhydramine: "Benadryl."
Meclizine: "Bonamine."
Doxylamine: "Decapryn."

MISCELLANEOUS OR NONSPECIFIC CENTRAL ACTIONS:

Meprobamate: "Miltown," "Equanil."
Mephenesin: ' Myanesin," "Tolserol," "Lissephen," "Oranixon."
Hydroxyzine: "Atarax."
Azacyclonal: "Frenquel."
Methyprylon: "Noludar."
Glutethimide: "Doriden."
Ectylurea: "Nostyn."
Ethchlorvynol: "Placidyl. '
Phenoglycodol: "Ultran."

2. Mechanisms of Action

In the laboratory the actions of meprobamate combine some of the features of mephenesin, barbiturates, and ethyl alcohol. The taming effect on hostile animals, such as monkeys, is easily demonstrated. Unlike reserpine and chlorpromazine, meprobamate has no notable autonomic blocking properties; it does not produce tremors or potentiate convulsions, and in fact gives some protection against metrazol-induced convulsions; in sufficient dose it causes sleep and anesthesia. It appears to depress all levels of function of the nervous system, and therefore should be classed as a general central depressant.

Attempts to localize further the mechanism of action of meprobamate have tended to implicate diencephalic centers. Hendley et al.[15] noted that the lateral relay nuclei of the thalamus were particularly depressed. Since this comprises part of the pathway for conscious sensation from the muscles, it is conceivable that the feeling of relief from muscle tension contributes to the reduction in anxiety tone.

D. Other Tranquilizers

The tranquilizers already mentioned are those which have been studied and used most extensively. The remainder do not fall into any easy classification compatible with our present understanding of mechanisms of tranquilization. However, a few are worth mention either because of wide usage or unusual modes of action.

1. **Hydroxyzine** is a sedative tranquilizer not intended for use in psychotic states, but probably of some value in a variety of tension states in ambulatory patients. Somnolence appears to be the chief complaint. Large overdoses have been accidentally ingested without fatality, so the margin of safety is relatively wide. Other important side-effects are yet to be described. Daily adult dosage is about 50 mg. per day. In the laboratory it appears to be nonspecific central depressant. In structure it resembles the antihistaminics.

2. **Azacyclonal.** In the search for new agents having central excitant properties similar to amphetamine, but devoid of the appetite-reducing feature, a new stimulant, pipradol, was introduced[11]. Concurrently an isomer of pipradol, azacyclonal, was studied because of its ability to antagonize the stimulant effects of pipradol[10]. Clinically azacyclonal appeared to be useful in initial trials in institutionalized psychotics. However, it now appears that the most valid use is as an anti-hallucinatory agent in such confusional states as post-alcoholic delirium tremens. In general, there has been sharp disagreement in the literature as to effectiveness and dosage. Some authors have reported favorable results with as little as 20 mg./day, and others have given up to 1000 mg. with no observable effect. At least the dose latitude is wide and toxicity negligible.

In the laboratory it is common to find that amphetamine-like molecules become depressant if the amine nitrogen is removed more than two carbons away from the aromatic group. Azacyclonal seems to be typical in this respect.

3. **Benactyzine.** In recent years there has been an interest in a class of drugs called potentiators, which increase the depressant potency of barbiturates, etc., while having no depressant action in themselves. Many of the tranquilizers, for example, chlorpromazine, are potentiators, and tests for this property are commonly used in the search for new tranquilizers. Potentiation is commonly found in many congeners of autonomic drugs, often in the antihistaminic and anticholinergic group. A number of potentiators have been found among aromatic alkylamine esters, structurally related to trasentin, and these often have atropine-like actions. Benactyzine belongs in this class. It has been extensively studied in Europe and used as a tranquilizer in milder neurotic states, but its principal indications are still uncertain. Dosage, 5-10 mg./day.

4. **Miscellaneous.** Tranquilizing actions have been claimed for many of the newer *non-barbiturate sedatives* such as methyprylon, phenoglycodol, glutethamide, ectylurea, ethchlorvynol, etc. It should be remembered that the barbiturates as a class have been for many years most widely used as tranquilizers in mental hospitals and, in fact, in almost every aspect of medical practice. Non-specific central depressants as a class are in demand on a wide scale, and perhaps we should include ethyl alcohol as the most widely used of all tranquilizers, at least in contemporary western culture.

It is interesting to note that the central depressant effects of some *antihistaminics*, for example, chlorcyclizine, have now been turned to advantage as tranquilizers. Imprisoned narcotic addicts have been known to excoriate their skin to justify a medical order for diphenhydramine or other depressant antihistaminics[21]. The antiemetic meclizine should probably be also included in this class.

IV. DISCUSSION AND CONCLUSIONS

If one must classify tranquilizers, the easiest breakdown would be into nonspecific central depressants *vs.* agents, not necessarily depressant, related to autonomic blocking drugs. The latter include members best classified as antihistaminic, anticholinergic, and antiadrenergic. Such a classification is attempted in Table 1 .

Most of the tranquilizers appear to be of some benefit in alleviating the tensions and anxieties of everyday life, and therefore are of value in the management of neuroses and in supportive treatment of a wide variety of ailments with psychogenic features. Judiciously prescribed they are usually relatively safe with regard to latitude of dosage and freedom from dangerous side-effects. Excessive central depression can be antagonized by typical analeptics of the amphetamine type.

However, many responsible physicians and scientists are uneasy about the tendency toward widespread and indiscriminate usage of tranquilizers. One problem concers the possible "behavioral toxicity" of all such agents, in the sense that some degree of anxiety is often essential to optimal performance in everyday life. It is therefore widely agreed that any trend toward over-the-counter nonprescription sale of tranquilizers should be discouraged, at least until more is known of the social price of pharmacological tranquility. Another area of concern is whether the long-continued use of tranquilizers in children may interfere with normal intellectual and emotional development.

The greatest therapeutic advance in this field has been the use of tranquilizers in institutionalized psychotics. Particularly in long-stabilized schizophrenics there has heretofore been no adequate therapy. It seems fruitless to debate whether the tranquilizers really attack the cause of schizophrenia. The practical result of social remission and discharge should be justification enough for use of presently available tranquilizers and a more intensive search for new and better pharmaceuticals.

It is interesting that the best results to date on severely disturbed institutionized patients have been achieved with agents which we would classify as adrenergic blockers, namely, the reserpine and chlorpromazine group. As a result there has been a great recent impetus toward studies in the biochemistry of schizophrenia, particularly around the question of possible distortions of metabolism of catecholamines and related substances. It is still premature to say that schizophrenia is a biochemical lesion. More likely it will be found, in the long run, that the etiology of schizophrenia (and of other behavioral syndromes) is manifold, but that certain final reaction patterns of distorted brain metabolism are resultant, and assist in sustaining the disease. If one can intervene at any convenient step to block the continuing pathological cycle, the intervention is medically justified. The success of treatment does not automatically explain the nature of the disease. As in so many other fields, theory runs considerably behind practice, and modern medicine still remains a largely empirical art.

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PITUITARY HYPOGONADISM IN THE MALE

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I.

Male hypogonadism may be primary, originating in the gonad itself, or it may be secondary, originating elsewhere in the body and affecting the gonads because of their dependence on certain outside factors. Examples of *primary* hypogonadism are furnished by any condition which can directly compromise the integrity of the testicles such as congenital absence, cryptorchidism maintained beyond puberty, castration, inflammatory processes due to mumps or other infectious diseases, tumors, trauma or surgery injuring the testicles or their blood supply. Foremost among those factors which can affect the gonads *secondarily* is the hypophysis through whose gonadotropic hormones the anatomical and functional maintenance of the seminiferous tubules and Leydig cell islets are achieved. These hormones, designated after their action in the female, are the follicle stimulating hormone (FSH), and the luteinizing hormone (LH), also called the interstitial cell stimulating hormone (ICSH). In the male FSH stimulates spermatogenesis in the seminiferous tubules, and LH stimulates androgen production by the Leydig cells.

Secretion of the gonadotropic hormones may be deficient because of a) manifest pituitary pathology injuring the anterior pituitary gland or adjacent hypothalamic area by tumor, abscess, hemorrhage, atrophy, or therapeutic hypophysectomy; or b) processes elsewhere in the body capable of adversely affecting pituitary functions. An example of the latter is hypogonadism developing in cases of prostatic cancer with metastases which are being treated with large amounts of estrogen leading to inhibition of pituitary gonadotropin production. It is known that testicular atrophy and other signs of hypogonadism may accompany hepatic (portal) cirrhosis; there is evidence that this is due to excess estrogen circulating in the body as a result of failure of the damaged liver cells to inactivate estrogens that are normally produced in small amounts in the male. Nutritional deficiencies, toxemias, and blood dyscrasias may cause hypogonadism by damaging the gonadotropin producing cells of the anterior pituitary. The hypogonadism found in some cases of myxedema is probably a mixture of testicular deficiency and decreased gonadotropin production in the anterior pituitary, as a result of the lowered cellular metabolism in both organs.

In this paper discussion will be limited to male hypogonadism due to manifest pituitary pathology. Although these cases are infrequently seen in general medical practice they are of considerable interest because they dramatically illustrate the operations of a glandular interrelationship in health and disease; furthermore, correct interpretation and diagnosis may be of great practical importance for the management of the patient.

II.

Since the normal mature testicles have two distinct functions: spermatogenesis by the seminiferous tubules, and secretion of the male sex hormone by the Leydig cells, hypogonadism may consist of 1) tubular deficiency resulting in oligo- or azoospermia, or 2) a-Leydigism resulting in deficiency or absence of male secondary sexual characteristics. Actually, in most cases of hypogonadism both functions are affected, although complete tubular deficiency may exist in the presence of normal Leydig cell function. On the other hand, severe a-Leydigism is almost invariably associated with some degree of tubular failure in view of the fact that male sex hormone is necessary for effective tubular function.

The *presenting symptom* of tubular deficiency usually is infertility. The patient may not be aware of the reduced

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size of the testicle which is the result of tubular atrophy; normally the tubules make up 2/3 to 4/5 of the testicular mass. If there is no accompanying Leydig cell deficieincy all secondary sexual characteristics may be normal.

In Leydig cell deficiency the presenting symptoms usually are those of eunuchoidism. This term is used here to denote the absence of the normal secondary sex characteristics of an adult male as seen in the body proportions, texture of skin, genital organs, prostate gland, male type of hairiness, larynx and voice, sexual impulse and potency. Eunuchoidism may be total, involving all secondary sex characteristics occurring when severe deficiency sets in some time before puberty. When deficiency develops post-pubertally, i.e. after normal sexual development had taken place, the reversal to prepubertal gonadal status may be but partial: the skeletal proportions remain normal, the voice may be but little affected, the external genitalia and sexual hair may retain some degree of maturity, and some sexual impulse and ability may remain as a result of earlier conditioning.

Some hypogonads seek medical attention primarily for symptoms other than those due to tubular or Leydig cell failure. Thus, if the gonadotropic failure is but part of a panhypopituitarism, the patient may present himself because of dwarfism, or extreme weakness or drowsiness, resulting from the deficiency in growth hormone, adrenocorticotropic or thyrotropic hormone.

III.

Diagnosis

The *history* may not only establish or suggest the existence of hypogonadism in the patient but may furnish important clues concerning the type—primary or secondary—of hypogonadism. Special efforts must be made to find out the time of onset of the signs and symptoms, the occurrence of trauma or disease of the genitals or intracranial structures, nutritional, endocrine or metabolis disturbances, chronic liver disease, administration of hormones and drugs or exposure to X-radiation. The history may help uncover similar or related anomalies in other members of the family.

Physical examination should include, in addition to routine general examination, measurement of height, weight and skeletal proportions; the body fat distribution; the mammary region; the external genitals; rectal examination for the prostate and seminal vesicles; the status of hairiness over the pubic region and lower abdomen, axillae, face, chest, extremities and scalp.

The main *skeletal* proportions in an adult are normal if height and horizontal reach are about equal, and if the upper body is as long as the lower, the pubis serving as a midpoint. In eunuchoidism originating prepubertally the reach usually exceeds the height, and the lower body exceeds the upper. This is due to delayed union of the epiphyses of long bones permitting a longer period of epiphyseal growth.

Disproportionate *fat* deposits about the pubic region, hips and buttocks may be a eunuchoid feature.

Transient *mammary* hypertrophy is not infrequently found in normal puberty of boys, and has no pathognomonic significance. Marked breast enlargement in the male beyond the age of 18, however, is abnormal. This gynecomastia may be a true one, consisting mainly of mammary tissue with an increase of the areolae and nipples, or may be pseudogynecomastia containing mainly an accumulation of fat. The differentiation without biopsy is not always easy; besides, both may be present in some patients. True gynecomastia rarely, if ever, is present in pituitary hypogonadism of organic origin.

Of special importance is a careful examination of the *genital organs*. Fat deposits in the pubic area may obscure a normal sized penis and give the erroneous impression of an infantile penis. On the other hand, an abnormally small penis may be present in men whose other secondary sexual characteristics are well developed indicating adequate androgen production; here one of the target organs, the penis, failed to respond to normal amounts of androgen. It appears that the penis is subject to marked variations in androgen responsiveness.

It should be recognized that the underdeveloped penis in these cases is a target organ phenomenon rather than the result of hypogonadism. The scrotum, the size and consistency of the testes and epididymis must be carefully examined and any abnormal finding in the scrotal sac noted.

The *hair* organ in the human is normally highly sensitive to the effects of androgen, and hairiness of the male is, therefore, a useful indicator of the presence or absence of normal amounts of circulating androgens in the body. One must recognize "place and time" factors in hair growth. The effects of androgen on the hair organ are different, quantitatively as well as qualitatively, depending on the regions in which the hair follicles are located. The *scalp* hair is in a class by itself in that growth of this hair is not stimulated, as is all other hair, by androgen; on the contrary, it is inhibited by androgen. The extent of this inhibition depends a) on the constitutional, hereditary sensitiveness of the scalp hair follicles to androgen resulting, in the presence of normal amounts of circulating androgen, in early extensive baldness in some men and abundant scalp hair throughout life in others; b) regional sensitiveness to androgen within the scalp, the temporofrontal regions being more sensitive to inhibition by androgen with less sensitivity of the vertex, parietal and occipital regions, in that order; c) the amount of circulating androgen. Commonly, in androgen deficiency, the temporofrontal recession of hair, which in normal males becomes noticeable soon after puberty, is missing, and frequently abundant hair all over the scalp is retained throughout life. Constitutional factors, however, as mentioned above, may produce this result in spite of normal androgen levels and, therefore, it must not be accepted in itself as evidence of eunuchoidism.

Before puberty all hairy regions of the *body* are covered with lanugoid hair. The transformation of this hair into terminal hair and the maintenance of terminal hair require androgen. Without androgen lanugoid hair remains as such throughout life, and terminal hair soon reverts to lanugoid hair. That constitutional factors are also important for body hair growth is shown by the observations that a) normal males having normal amounts of androgen may differ greatly in general, as well as in regional body hairiness; b) in the same person certain hairy regions are much more sensitive to the hormone than are other regions. The *sequence* in the regional appearance of terminal hair at puberty and during later years is another expression of target sensitiveness to androgen. First to appear, responding earliest to the least amounts of androgen, is pubic hair; this is followed by axillary hair, later by hair over the upper lip, then chin and cheeks; next, in some men years later or never, over the chest, lower and upper extremities; and many years later over some parts of the ears and in the nose. A similar order is usually seen when eunuchoids having little or no body hair receive prolonged treatment with androgen; and the reverse sequence is observed when eunuchoidism develops in formerly normal adult males: first and most extensively the hair over the extremities and chest is lost, later and less completely the axillary, pubic and facial hair, in that order.

Examination of the hypogonadal patient should include a study of his *personality and emotional life*. Most hypogonad men are 'peculiar people.' Boys missing the changes of puberty which they observe in their friends are prone to develop a more or less thwarted personality manifested in inferiority complexes — sometimes overcompensated by false self-assurance and aggressiveness—frustration, over-sensitivity, resentment, suspiciousness and embitterment. Similar, and occasionally even more marked, emotional and behavioral anomalies develop in men in whom reversion to a prepuberal state occurs after years of normal sexual appearance and activity.

X-ray films of the skull may show intrasellar or suprasellar tumors, cysts, calcifications, xanthomatous changes in the floor of the sella —important findings for the diagnosis of pituitary pathology. Unfortunately, in cases of pitui-

tary atrophy or small tumors that do not expand the sella, X-ray studies of the skull may not be contributory. Films of the epiphyses of bones, especially of the hand, wrist and long bones, may show open junctions at ages well beyond normal fusion—an important sign of male hypogonadism that originated before pubertal age. Marked generalized osteoporosis may support the diagnosis of hypogonadism.

Specimens of *seminal* discharge are frequently not obtainable in pituitary hypogonadism because of failure of the erection and ejaculation apparatus. When obtainable they usually show a gross departure from the normal. In repeated examinations of seminal fluid obtained after 3-4 days of abstinence the *normal* volume is 3-5 cc, the average number of spermatozoa is 120 million per cc., the majority are motile, and abnormal forms do not exceed 25%.

Assays of the 17-*ketosteroids* in the 24 hour urine are less important for the diagnosis and differential diagnosis of male hypogonadism than they are in certain other glandular disorders. These steroids are mainly metabolic end-products of androgens. Normal adult men excrete daily 10-20 mg. in the urine, 1/3 of which are thought to be derived from Leydig cell androgen and 2/3 from adrenocortical androgen. Accordingly, 17-ketosteroids are not entirely absent in male hypogonadism unless there is an associated adrenocortical failure, and their excretion may be low in various types of adrenocortical deficiency without hypogonadism. On the whole, the clinical picture of eunuchoidism is a more reliable and sensitive indicator of Leydig cell deficiency than the urinary 17-ketosteroids.

Much more important for the diagnosis of pituitary hypogonadism may be *assays* of the *gonadotropic hormones* excreted in the urine. In pituitary hypogonadism these hormones are absent or greatly decreased indicating failure of the pituitary cells which normally produce gonadotropins. In hypogonadism due to primary failure of the testicles urinary gonadotropins are excreted in normal or increased amounts indicating that the pituitary gonadotropic apparatus is intact. Especially in those cases of hypogonadism in whom signs of thyrotropic or adrenotropic deficiency are not demonstrable and X-ray films of the sella are non-contributory, assays of gonadotropin excretion are invaluable in differentiating between primary and pituitary hypogonadism. Unfortunately this assay is difficult to carry out with sufficient accuracy and is rarely done outside of research laboratories. A fairly useful substitute can be resorted to in the form of a short therapeutic trial with commercially available gonadotropic preparations. For this purpose chorionic gonadotropin, 5,000 units, may be given intramuscularly twice weekly for 2-4 months and effects on the scrotum, penis, pubic and axillary hair observed. Noticeable effects indicate androgen production by the Leydig cells in response to gonadotropic stimulation, and hence, are incompatible with primary hypogonadism. Lack of effects indicates inability of the Leydig cells to respond to gonadotropic stimulation and therefore favors the diagnosis of primary hypogonadism. Even more useful are assays of the urinary 17-ketosteroids before and after a few days' daily administration of chorionic gonadotropin, increased excretion militating against primary hypogonadism, no change in the excretion speaking for primary hypogonadism.

Testicular biopsy. According to Albert et al.[1] "testicular biopsy in conjunction with the general examination of the patient provides a reliable, accurate, rapid and inexpensive single laboratory procedure for obtaining routinely all the information that is necessary for the correct management of hypogonadal disease of the male." On the other hand, Sand and Okkels[2] warned that too rigid a reliance on histologic interpretation alone can be misleading. They have examined the testicles of 72 normal males subjected to legal castration or violent sudden death, and found that over 75% showed abnormal histology such as thickening of the tubular basement membrane or thickening and hyalinization of the intertubular tissue, and in 20% spermatogenesis was markedly reduced.

In our own experience, in most cases of hypogonadism, testicular biopsy did not furnish important information which was not readily obtained by the history and other examinations. Biopsy is rarely needed to evaluate prognosis of infertility inasmuch as the seminal discharge is as good, if not better, an indicator, complete or almost complete, consistent azoospermia suggesting an unfavorable prognosis while minor or moderate degrees of hypospermia justifying institution of corrective measures. Attempts to definitely differentiate certain types of primary tubular failure from the testicle of pituitary hypogonadism on the basis of the histologic picture have not proved satisfactory. Furthermore, many patients refuse to permit a testicular biopsy. Nevertheless in special cases biopsy is invaluable. For instance, when azoospermia exists in the presence of testes of normal size, only a biopsy can differentiate between seminiferous tubule failure and obstruction of the excretory ducts—a distinction of obvious practical importance.

Among *other laboratory studies* those to test thyroid and adrenocortical activity may yield important information as to the origin of the hypogonadism. These may include BMR, I^{131} uptake by the thyroid, PBI^{131} in the blood, PBI in the blood, the eosinophile response to ACTH (modified Thorn test), 11-oxysteroids in the blood or urine, serum electrolytes, blood sugar, etc. The demonstration of thyroid or adrenocortical failure strongly supports, although not necessarily proves, pituitary origin of the hypogonadism. On the other hand, normal thyroid and adrenocortical activity does not exclude such an origin since pituitary failure may be unitropic, i.e. limited to impaired production of gonadotropin only.

IV.

Therapy

Most cases of secondary (pituitary) hypogonadism present special therapeutic problems; only the main lines of therapy will be discussed here. In general, therapeutic efforts are directed along two lines: 1) to relieve, if possible, the causative pituitary pathology, and 2) to correct by direct approach the signs and symptoms of the hypogonadism.

Concerning the first task, in frank pituitary pathology (tumor, cyst, hemorrhage)—especially in the presence of serious sequelae such as increased intracranial pressure or visual disturbance due to chiasmal pressure—surgery or X-radiation of the pituitary region is to be considered. If hypogonadism is but part of panhypopituitarism, the accompanying thyroid or adrenocortical failure must be treated. If the pituitary deficiency is a result of malnutrition or toxemia of recognizable origin, measures to relieve these conditions must receive attention.

Treatment of the hypogonadism itself by gonadotropins has not proved satisfactory. One of the two main elements of hypogonadism, Leydig cell failure, is due to luteinizing hormone deficiency, and was expected to be amenable to chorionic gonadotropin therapy, as this gonadotropin is rich in luteinizing hormone. The other main element of pituitary hypogonadism, seminiferous tubule failure, was expected to respond to potent preparations of FSH, and preparations of pregnant mare serum containing FSH in moderate potency are available. Both of these extracts, however, are antigenic giving rise to antibodies after a series of injections and thus lose their effect. Little would be accomplished by a brief, temporary correction of the deficient secondary sexual characteristics. On the other hand even a temporary successful stimulation of the seminiferous tubules with improvement in the number and quality of the spermatozoa might lead to fertility and conception; such successes have been reported. In cases of milder degrees of tubular deficiency showing sperm counts of 20-50 million per ml. a trial with pregnant mare serum gonadotropin may be justified.[3] Such cases of tubular deficiency can be treated more successfully with androgens. Large amounts of this hormone administered over a period of 1-2 months are known to inhibit spermatogenesis, but later there may follow a rebound stimulation of the seminiferous tubules resulting in

sperm counts and quality much above the pre-treatment level.[4] Improvement may last for a considerable length of time and may be produced repeatedly. Androgen therapy is eminently successful in developing the secondary sexual characteristics that are absent or deficient in Leydig cell failure. Relatively small amounts are required for this purpose at early post-pubertal ages, and progressively greater amounts are needed with advancing age. For lasting results this treatment must, of course, be continued indefinitely. In the elderly eunuchoid effective androgenic stimulation is not desirable, and the presence or absence of secondary male characteristics has lost its earlier psychological or social importance. Osteoporosis may remain his only serious drawback, but that can be successfully treated with administration of estrogen.

V.

Four types of pituitary hypogonadism observed by us will be described and analysed.

Case 1. *Pituitary hypogonadism with dwarfism due to cranio-pharyngeal cyst.*

H.M., a 26 year old midget, sought medical attention because of genital infantilism. He wanted to look and act like a male as he had plans to marry a midget girl. He had no desire to grow, thinking there might be a definite advantage in remaining short and capitalizing on his stature for employment.

History: There were no cases of gross abnormalities in his family. His father, mother and sister were of normal height and weight. His gestation and delivery were uneventful, and he weighed 7 lbs. at birth. He seemed to grow normally until he was about 4 years old, walked and talked at normal age, and the eruption of the deciduous teeth followed a normal pattern. The eruption of the permanent teeth was delayed because of retention of the deciduous teeth. Finally, almost all deciduous teeth had to be extracted upon which eruption of the permanent teeth followed in due order. He continued to grow at a very slow rate, at about a quarter of an inch yearly during the past 5 years. He finished high school at 18 and entered college at 21. The first manifestations of puberty such as sex interest and erections occurred at 15; however, the genitals remained infantile, he failed to develop pubic, axillary and facial hair, and never shaved. Aside of minor childhood diseases he always enjoyed good health. He had an active life as a successful salesman.

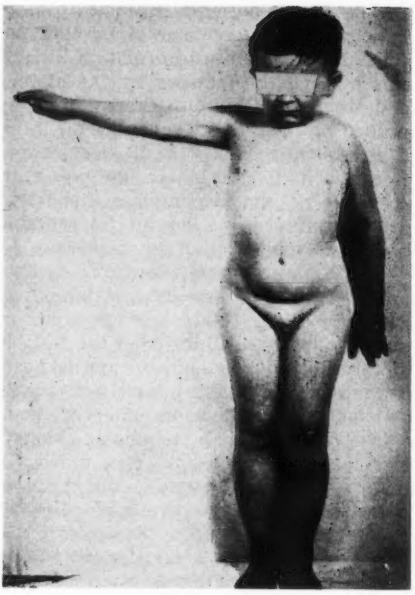

FIGURE 1

Examination: His general appearance was that of a 10 year old boy. (Fig 1.) Height 52.5 inches, span 52 inches, weight 69 lbs. The skin was soft with somewhat increased subcutaneous fat deposits, especially in the girdle and pubic region. The penis was infantile. Both testicles were found in the scrotum and measured about ⅞ by ⅝ inches which would be normal for a 12 year old boy, at the beginning of puberty. The prostate and seminal vesicles were not palpable on rectal examination. The face looked infantile and progerial (*wizened*) at the same time. He had abundant dark scalp hair without any temporofrontal recessions. His teeth were fairly well developed without

noticeable malocclusion; there was much dental work; all permanent teeth were present including the second molars; the third molars were unerupted. No pubic, axillary, chest, facial, or other body hair was visible. The thyroid was not palpable. The voice was infantile. He was mentally alert, intelligent, with a pleasant but self-assertive behavior. His basal oxygen consumption was 128 cc. per minute which yields a BMR of about minus 16% if compared with his "normal standard" of 153 cc. per minute. The blood pressure was 98/68. The fasting blood sugar was 118 mgs percent, and an oral glucose tolerance test was within normal limits. The blood cholesterol was 189 mgs percent. X-ray films of the hand revealed that all epiphyseal junctions were still open; his bone-age was 14 to 15 years. (Fig 2) Films of the skull showed that the frontal sinuses were absent; the maxillary, ethmoid and sphenoid sinuses were well developed and clear. The facial area was small as compared with the size of the skull. The sella turcica appeared to be normal in size, and its floor and clinoid processes were intact. A half-moon shaped area of increased density 1.5 cm by 0.75 cm is seen above the sella—a finding characteristic for cranio-pharyngeal cyst. (Fig. 3) The optic fundi and visual fields were normal.

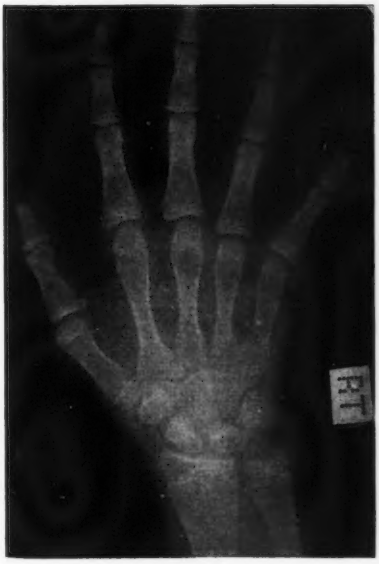

FIGURE 2

Comment

Minor or moderate degrees of associated somatic and genital underdevelopment may occur as a result of cretinism or other forms of early hypo-thyroidism, various types of malnutrition, poorly controlled juvenile diabetes etc., and may then pose problems of differential diagnosis. However, infantile hypo-thyroidism severe enough to produce a growth disturbance and hypogonadism of a degree seen in this patient would not be compatible with this patient's mental alertness and intelligence. The history does not reveal any severe nutritional or metabolic deficiency in this case. Accordingly, the history and physical examination in themselves, without any laboratory studies, would be sufficient in this case to arrive at the diagnosis. The X-Ray films of the skull not only confirmed the pituitary origin but disclosed the nature of the pituitary pathology.

Pituitary dwarfism with genital infantilism is usually a part of panhypopituitarism, i.e. it is associated with deficiency of the other main anterior lobe hormones, the thyrotropic and adrenotropic hormones. In cases where assays of these hormones were made along with studies of the functional capacity of the thyroid and adrenal cortex, these deficiencies were clearly demonstrated.[5] Nevertheless, in the clinical picture of most of these cases, as well as of our case, these deficiencies are much less evident than the deficiency of the growth- and gonadotropic hormones. Many pituitary dwarfs showing I^{131} tests typical for hypothyroidism, and serum electrolytes, eosinophile response and other tests typical for adrenocortical deficiency, live an active physical and intellectual life. This is in sharp contrast to Simmond's disease or other forms of panhypopituitarism developing in adulthood: they are mentally dull and physically incapacitated. Possibly, one reason for this difference lies in the fact that in the pituitary dwarf the thyroid and adrenocortical deficiencies develop slowly in

childhood, i.e. at a period of life when the adaptability of the tissues is greater enabling the cells to learn to function satisfactorily in the presence of lessened amounts of necessary hormones.

After the patient was informed about the limitations of therapeutic results he was given intramuscular injections of testoterone propionate, 25 mgs in oil, twice a week, for 4 months. There was marked growth of the external genitals; pubic hair and axillary hair appeared; his voice changed noticeably; frequent, strong erections of the penis with some libido occurred. He grew almost 1 inch and gained 4 lbs. Treatment then was discontinued as he lost interest in therapy in view of the fact that the little lady—who was a "primordial dwarf" i.e. one with entirely normal glandular system—refused to marry him. When last seen, 6 months later, there was a regression of all secondary sex characteristics to almost the original status.

Case 2. *Hypogonadism due to idiopathic gonadotropic failure.*

W.B., a 23 year old artist, came to Mount Sinai Hospital Clinic because of failure to mature genitally. Aside of measles, chicken pox and whooping cough in childhood, he was always well and healthy. His genital organs remained infantile, there was no pubic or axillary hair, and he never shaved. At the age of 19, a physician gave him a series of injections of chorionic gonadotropin for a period of 4 months which resulted in slight increase in the size of the penis and some growth of hair in the pubic and axillary region; these effects were not maintained after treatment was discontinued. He never engaged in any sexual activity.

Examination showed a tall boy who looked younger than his age. (Figure 4) He weighed 198 lbs., height 74 inches, reach 75 inches. The voice was high pitched. The hands and fingers were long and narrow. The penis and scrotum were infantile, both testicles prepubertal. There was a small amount of pubic hair with a female type escutcheon, and no axillary, facial or chest hair. The scalp hair was abundant with no temporofrontal recessions. There was no gynecomastia. The prostate gland and seminal

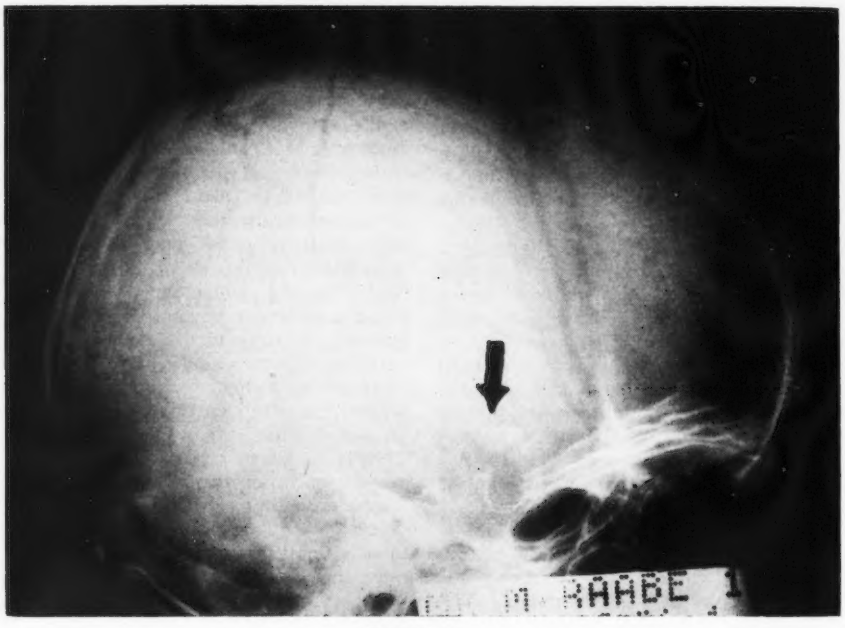

FIGURE 3

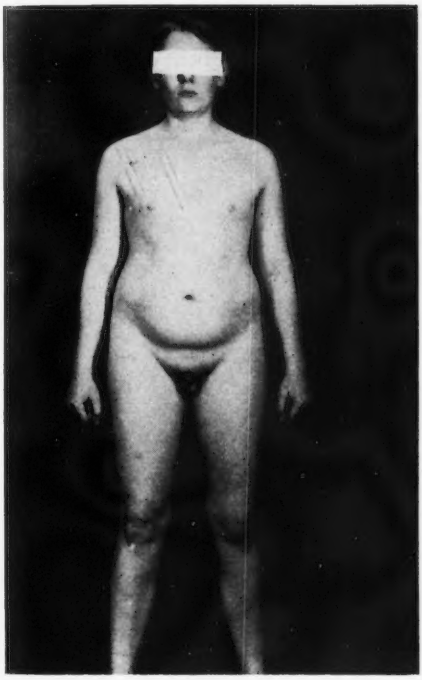

FIGURE 4

vesicles were not palpable on rectal examination. The thyroid was barely palpable.

BMR was minus 6%. The total blood cholesterol was 242 mg per cent; the I^{131} in the blood 0.017 μc/L—all within normal limits. The fasting blood sugar was 102 mg. per cent, and an oral glucose tolerance test was normal. The 24 hour urinary 17-ketosteroid excretion was 13.5 mgs—which is a low normal figure for his age; 24 hour urinary gonadotropins: 0. X-Ray films of the skull showed no abnormalities; the sella turcica was of normal size and configuration. Films of the hand showed all epiphyseal junctions closed, but the lines of closure were still visible over several junctions. Testicular biopsy (Fig. 5) shows that most tubules are reduced in size; the tubular wall is generally thin, immature, although in some tubules it is thickened. Two or three rows of spermatogonia but no spermatocytes are seen in most tubules, and the wide, empty lumens contain no spermatozoa. The interstitial tissue is sparse and contains no Leydig cells. Seminal discharge was not obtainable.

Comment

On the basis of the history and physical examination alone, this case could be assumed to be one of primary hypogonadism, of the group that Heller and Nelson described as "Puberal seminiferous tubule failure."[6] This group includes besides the original Klinefelter-Reifentein-Albright types—which have gynecomastia, small testes, azoospermia and well developed secondary sex characteristics—cases with small testes and azoospermia but without gynecomastia and with more or less marked eunuchoid features. This patient would seemingly fit in the latter type. The normal thyroid and normal adreno-cortical functions as indicated by the laboratory tests, and the negative skull films would be consistent with this diagnosis. However, three tests tend to disprove this possibility, and allow definitely to classify the case as pituitary hypogonadism: 1. The (temporary) effectiveness of chorionic gonadotropin therapy. This does

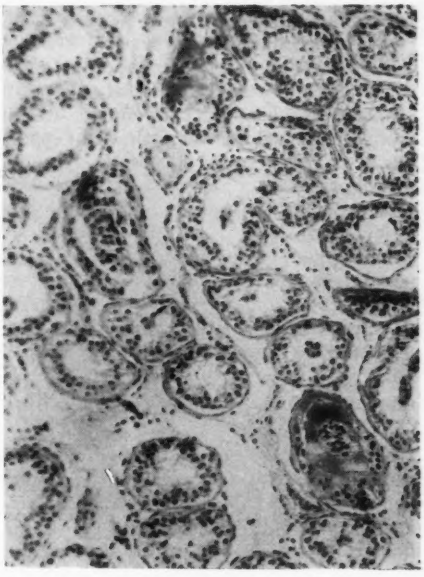

FIGURE 5

not occur in primary hypogonadism but may be found in pituitary hypogonadism. 2. The testicular biopsy commonly shows fibrosis or sclerosis of the seminiferous tubules and a normal or increased number of Leydig cells in the Heller-Nelson types of primary hypogonadism; neither of these findings were present in our case. The main finding of the biopsy in pituitary hypogonadism starting prepuberally is: immaturity of the tubules and interstitial elements, and this was present in our case. 3. The gonadotropin titer is normal or high in all cases of primary hypogonadism, and low or zero in pituitary hypogonadism; it was zero in this patient.

The nature of the pathological process in the anterior pituitary in these patients is not known as no biopsies or autopsies of the pituitaries of such cases are available. Conceivably, there might be agenesis of the gonadotropin producing cells with normal development of the other hormone producing cells or, as Albert et al[7] speculate some specific enzyme system necessary for the elaboration of gonadotropin may be deficient.

For therapy the patient was given intramuscular injections of testosterone propionate, 100 mgs in oil, twice a week for a month, later 50 mgs. twice a week, which he soon learned to administer to himself. After a few months of this treatment there was marked change in all secondary sex characteristics: the penis grew to almost normal size, there were frequent, strong erections, his voice changed, pubic and axillary hair developed and he shaved twice a week. He got married and reported that he had regular sexual relations with libido but without seminal discharge. He continues to give himself injections of a depot-testosterone preparation twice a month with sustained good results.

Case 3. *Pituitary hypogonadism due to intrasellar tumor.*

N.D., a 60 year old business man presented himself because of dizziness and weakness of hands fearing a "paralytic stroke." He said he had a normal childhood until the age of 10 when he stopped growing. His genitals remained small, he never shaved and had no sexual manifestations of any kind. He did well in elementary school excelling in spelling and algebra, but higher education was denied him as he had to go to work. His height was 4 feet and 10 inches when he was 23 years old but then he began to grow faster again and reached his present height of 5 feet 4 inches about ten years later. He had anosmia all his life. He had "flashes of light" before his eyes three years before admission but eye examination at that time showed nothing abnormal.

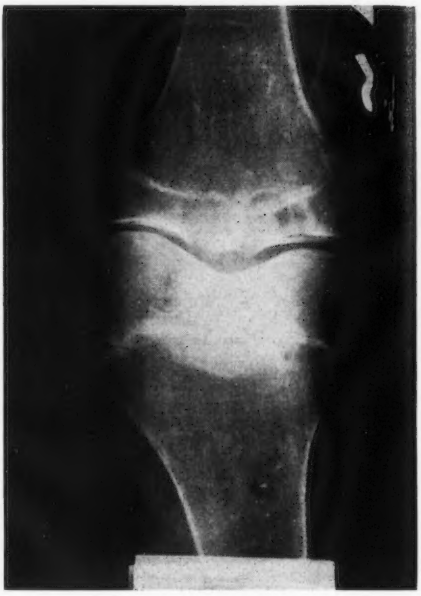

FIGURE 6

Examination disclosed an elderly man with a high pitched voice and wizened, pale, yellowish skin, sparse eyebrows, wrinkled puffy eyes who looked like a mixture of eunuchoidism and myxedema. His height was 5 feet and 4 inches, and he weighed 135 lbs. His ears, hands and feet were disproportionately large, wide and heavy, in contrast to the narrow hands and feet of the average eunuchoid. The shoulders were narrow compared with the wide girdle which showed marked fat deposits. There was some pseudo-gynecomastia. The penis and scrotum were prepubertal; both testicles were in the scrotum and had the size of

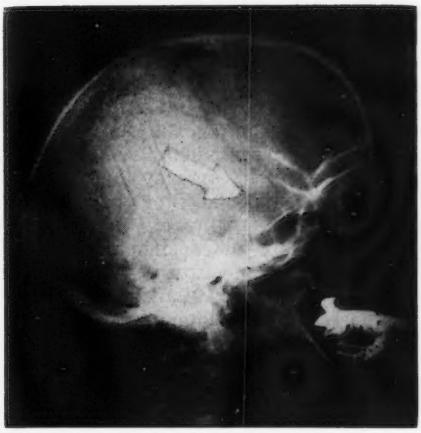

FIGURE 7

large peas. The prostate and seminal vesicles could not be felt on rectal examination. No hair was visible in the pubic region, axillae, chest and face, but the graying scalp hair was abundant without temporal recessions. The rest of the physical examination was not remarkable. Examination of the eyes was reported as normal except concerning the visual fields: there were upper temporal defects in both the right and left fields indicative of median chiasmal pressure from below.

The BMR was minus 6%. Blood cholesterol 414 mg. per cent. The 24 hour urinary 17-ketosteroids were 1.5 mg. (normal at that age, 10 to 14 mg.). The 11-oxysteroids in the blood were 17 microgm. per cent (normal, 12 to 25). Serum proteins and electrolytes were within normal limits. Urinalysis was normal. The differential blood count showed 8% eosinophils, the blood count was otherwise normal. An I^{131} uptake test was interpreted to indicate euthyroidism. The Thorn test was negative, i.e. showed no decrease in the number of circulating eosinophils after injection of ACTH (355 per cmm before, 361 after ACTH). X-Ray studies showed incompletely fused epiphyses at the distal ends of the radius and femur, and at the proximal end of the tibia (Fig. 6), with generalized osteoporosis. The sella turcica showed marked widening of the AP diameter with destruction of the anterior clinoid processes. (Fig. 7 and 7a, the latter a close-up.)

Comment

Hypogonadism of pituitary origin due to intrasellar tumor was readily diagnosed in this case. The simultaneous occurrence of growth disturbance and hypogonadism strongly suggested hypopituitarism, the extremely low 17-ketosteroid excretion and the negative Thorn test as evidences of adrenocortical deciency supported this diagnosis, and the X-Ray findings in the skull and the characteristic visual field defects proved the presence of pituitary tumor. There is no doubt that this tumor had existed since

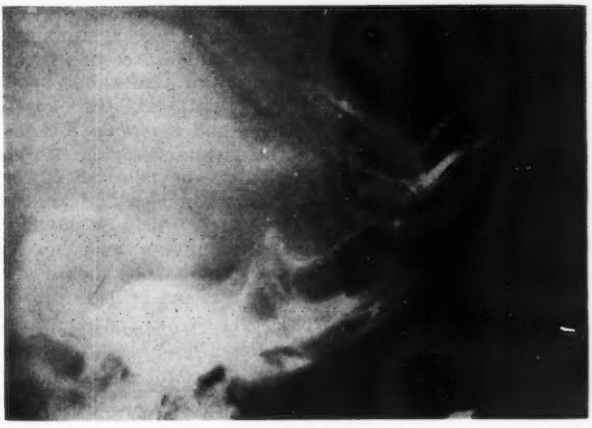

FIGURE 7A

childhood, but its presence and role in the eunuchoidism of the patient was not recognized before admission although X-Ray pictures of the skull would have easily lead to the correct diagnosis.

Some pertinent questions still remained to be answered. What is the explanation of the unusual history of skeletal growth in this patient, i.e. practical cessation of growth at 10 years of age, very slow growth later until 23, additional faster growth during the following years and some acromegaloid growth thereafter? What kind of tumor could produce such a picture? Bailey and Cushing[8] described a number of cases of hypopituitarism due to chromophobe adenoma who showed mild features of acromegaly. The microscopic picture of the tumor in these cases was characterized by evidence of some eosinophilic cellular activity, fine alpha granules appearing as a ring in the peripheral cytoplasm; thus, these cells had the structure of embryonic eosinophilic cells. Bailey and Cushing suggested that pituitary tumors producing the combined picture of hypo- and hyperpituitarism represent specific mixed adenomas in which the alpha cells remained embryonic in type. Soffer[9] lists 3 patients with chromophobe adenomas showing evidences of hypopituitarism mixed with acromegaly. He reports that careful histologic study of these tumors failed to reveal the presence of any kind of eosinophilic cells, all cells being typically chromophobic. Soffer suggests that the hyperpituitary signs may have resulted from the irritative pressure of the tumor on the adjacent cells, originally stimulating them to increased secretion and only subsequently producing atrophy. Chromophobe tumors of the pituitary usually occur in adults, and all these patients of Bailey and Cushing and of Soffer were adults—with the epiphyseal junctions closed—when the first signs of pituitary disease appeared; none of them showed stunted growth followed by late epiphyseal growth. However, when chromophobe adenoma develops in a child—which does occur although very rarely—the resulting growth hormone deficiency causes stunted growth, and the simultaneous hypogonadism keeps the epiphyseal junctions open for many years. If then, in adulthood, growth hormone producing eosinophilic cells emerge this will lead to late epiphyseal (statural) growth and, still later after the final closure of the epiphyseal junctions, to acromegaloid growth. It may be assumed that this happened in our patient. The nature of the process that has led to a revival of the eosinophils in this tumor remains obscure. A "mixed adenoma" of the type Bailey and Cushing described, developing in childhood, would allow normal or accelerated somatic growth rather than produce stunted growth. Neither can Soffer's assumption be applied in view of the fact that in our patient hypopituitarism developed early, and hyperpituitarism followed many years yater. Conceivably, a small number of eosinophils escaped destruction by the pressure of the chromophobe cells and produced enough growth hormone for very slow somatic growth as long the the epiphyseal junctions remained open; then, for some unknown reason, a hyperplasia of eosinophils took place producing the acromegaloid features. This could probably occur in other than chromophobe tumors, e.g. in craniopharyngiomas which are much more common in childhood.

In therapeutic considerations for this patient the main question was: was there danger of further encroachment of the optic chiasma by the tumor? Since the patient had no visual complaints nor signs or symptoms of increased intracranial pressure it was decided to keep him under observation repeating the visual field tests at frequent intervals, and resort to X-Ray irradiation of the pituitary region if and when extension of the field defects or signs of increased intracranial pressure would develop. At his age gonadotropin or androgen therapy was not indicated. For the extensive osteoporosis an oral estrogen was prescribed.

Case 4. *Hypogonadism with multiple defects of pituitary function possibly due to tumor.*

J.L., a 41-year-old man presented himself at Mount Sinai Hospital Clinics

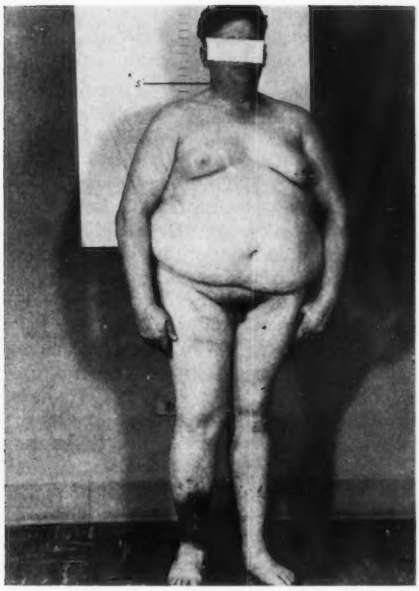

FIGURE 8

because of extreme overweight. When six years old he suffered a blow to the genital region while playing, and the organs became red and swollen. He noticed later that his genitals "did not grow"; they remained small all his life. At the age of 17 to 19 he had some "pimples" over his face, erections of the penis and a few nocturnal emissions but none after he was 20 years old. At the same time he developed some hair over the pubic region, upper lip and chin, and began to shave; he shaves twice a week. He was not obese until after 20, and then gained weight gradually year after year. He had very little education; he quit school after 3 or 4 years in elementary classes because he "couldn't keep up with the other children." He was unemployed most of his life because "they don't want to hire a fat man." He had no sexual experiences of any kind.

Examination disclosed a tall, very obese man who looked younger than his age. There were especially great fat deposits in the abdomen. He had a high-pitched, immature voice. His weight was 315 lbs., height 6 feet 2 inches, reach 6 feet 4 inches. The hands were large and heavy. The penis and scrotum were prepubertal, the right testicle had the size of a navy bean, the left the size of a large pea. There was scanty pubic hair of the female type, very sparse axillary hair, no chest hair and scant facial hair. He had abundant dark scalp hair without temporal recessions. There was marked bilateral pseudo-gynecomastia. (Fig. 8). The blood pressure was 140/72. There was stasis dermatitis on the right lower leg. Physical examination was otherwise not remarkable. Urine examination was negative. A hemogram was normal. Blood chemistry including sugar, proteins, urea nitrogen, uric acid and electrolytes was within normal limits. The blood cholesterol was 270 mg. per cent. An oral glucose tolerance test showed 250 mg. per cent blood sugar after 1 hour with sugar in the simultaneous urine specimen, but was otherwise within normal limits. BMR was plus 2 per cent. A Thorn test was done with the following result: circulating eosinophils 111 per cmm of blood; 4 hours after i.m. injection of 40 mg. ACTH, 131. This was interpreted to indicate "no adreno-cortical response." The results of a gonadotropin test for 17-ketosteroid response is shown in Table 1. It is seen that after administration of large amounts of chorionic gonadotropin for 6 days there was a marked increase in the urinary 17-ketosteroids.

This was interpreted to prove that the Leydig cells were fully capable to respond to gonadotropic stimulation. A radio-iodine test showed: I^{131} uptake by the thyroid, 3.6% (normal, 10 to 45), PBI^{131} inthe blood, 0.003 μc/L (normal, 0.008 to 0.05). This was interpreted as indicative of thyroid deficiency. The

TABLE 1

Date	injected chorionic gonadotropin units	17-ketosteroids mg. per 24 hour urine
Jan. 28	——	10.8
Jan. 29	1000	
Jan. 30	1000	
Jan. 31	1000	
Feb. 1	1000	
Feb. 2	——	
Feb. 3	5000	18.6
Feb. 4	——	23.0

gonadotropin titer of the 24 hour urine was more than 3 units and less than 6 units (normal values for adult males, 6 to 50 mouse units). Blood smears tested for genetic sex showed that the patient was a genetic male. X-Ray films of the skull showed marked hyperostosis frontalis interna with osteoporosis of the frontal and parietal bones; the facial bones were prominent with some prognathia of the jaw, the sella turcica was of normal size and configuration. Films of the hands and long bones showed complete ossification of the epiphyseal junctions; there was little, if any, osteoporosis. Retinoscopy showed normal fundi. The visual fields were normal.

Comment

In this case it was not possible to differentiate between primary and secondary (pituitary) hypogonadism without the help of newer laboratory tests. The history, physical examination, blood chemistry, BMR, X-Ray findings were all compatible with primary hypogonadism; only the presence of subnormal mentality and the acromegaloid features seemed to be out of line. The radio-iodine uptake test and the Thorn test indicated thyroid and adreno-cortical deficiency which do not belong in the syndrome of primary hypogonadism but may represent associated defects in pituitary hypogonadism. The response of the Leydig cells to injected chorionic gonadotropin was clearly incompatible with primary hypogonadism, and the decrease of endogenous gonadotropin in the urine confirmed the diagnosis of pituitary hypogonadism.

Some of the findings deserve special comment. The BMR was within normal limits in contrast to the radio-iodine test which definitely indicated hypothyroidism. It is known that the BMR as determined in the conventional test may be found high (plus 30% or more) in extreme obesity without thyroid disturbance, especially in patients with large abdominal fat deposits, because of the dyspnea of these patients with increased respiratory and cardiac action in the horizontal position which they must maintain during the test.[10] Accordingly, a "normal" metabolic rate may be found in such patients by the usual test when the truly *basal* metabolic rate (as determined in a respiratory chamber) would be low.

The negative Thorn test in this case, as well as in Case 3, is also seemingly out of line with the diagnosis of pituitary deficiency. Negative Thorn test, i.e. failure of the adrenal cortex to respond to stimulation by ACTH as judged from the unchanged eosinophil count, is characteristic for primary adreno-cortical deficiency (as in Addison's disease); while in adreno-cortical deficiency of pituitary origin a positive Thorn test, i.e. more than 50% decrease in the eosinophils would be expected. However, we now know that when secondary adreno-cortical atrophy has existed for a long time in a patient prolonged treatment with ACTH may be necessary to revive the adrenal cortex so as to enable it to produce good eosinopenic response to a subsequent ACTH injection. Therefore, lack of adreno-cortical response to one injection of ACTH in these patients, without previous conditioning with ACTH, does not necessarily indicate primary adrenal deficiency.

The history of trauma to the genital region seemed significant—and suggestive of primary hypogonadism — until more and more evidences of pituitary disturbance accumulated. No details concerning the extent and seriousness of the trauma could be obtained, and we have little doubt that it was incidental and played no major role in the picture. The chorionic gonadotropin test as shown in Table 1. conclusively proves that this was not a primary hypogonadism.

A test for genetic sex was made as part of our routine study performed at present in all cases of major gonadal disturbance. Following the observations of Barr and Bertram in 1949[11] on the nerve cells of cats, several workers have shown that the sex of many mammals including man can be clearly identified from the microscopic appearance of the cells of various tissues. Davidson and Smith[12] showed that there is a characteristic morphologic sex difference in neutrophil leukocytes of normal individuals. This has been confirmed by other work-

ers and using a similar technique, we have been able to identify the sex of normal males and females from their blood smears with 100% accuracy. It was shown by several investigators that in pseudohermaphrodim and gonadal hysgenesis the genetic sex may not be identical with the gonadal sex; thus, the majority of cases of ovarian dysgenesis (Turner's syndrome) were found to be genetic males[13], and the majority of cases of Klinefelter syndrome, genetic females[14]. It has been suggested that certain morphologic patterns in the nuclei of neutrophil leukocytes may be related to pituitary or other endocrine dysfunction[15]. In case No. 4 we found the genetic sex to be male. This is expected to be the finding in all cases of secondary male hypogonadism and in many cases of primary male hypogonadism. On the other hand, female genetic sex found in a male hypogonad would be strongly in favor of primary hypogonadism.

In this patient, as in Case 3, acromegaloid features,—large, heavy hands and feet, prominent facial bones, slight prognathia of the jaw—were observed in the presence of signs of marked hypopituitarism. This syndrome is similar to the one observed by Bailey and Cushing[8] and found by them to be due to a specific type of chromophobe adenoma. (See *Comment*, Case 3). The absence of an enlarged sella turcica, however, is a point strongly against the diagnosis of chromophobe adenoma, as is the absence of visual field defects. On the other hand, intra- or extrasellar tumors have been occasionally observed that had damaged pituitary functions without expanding the sella or compressing the optic chiasma; therefore, this case may be listed as "possible chromophobe adenoma." The excessive obesity of this patient suggests hypothalamic involvement which could be due to a neighborhood effect of the tumor rather than focal pathology in that area.

There was no indication for surgical approach in this case. Neither was effective androgenic therapy advisable for this 41 year old man of very low intelligence, in view of possible dubious effects on his psychological and social behavior. His therapy consists of low caloric diet and small amounts of thyroid substance and cortisone.

Summary

Hypogonadism due to failure of the anterior pituitary to secrete gonadotropins in amounts needed to develop and maintain testicular functions can appear in various clinical forms depending on a number of factors. Four cases observed by us in the clinic and in private practice representing different manifestations and pathology have been described and analysed. The diagnostic importance of certain hormone assays was emphasized along with the fact that in some cases a careful history, physical examination and conventional tests are quite sufficient to lead to the correct diagnosis.

We wish to thank Dr. Benjamin Blivaiss, Associate Professor in Physiology, The Chicago Medical School for his assays of the 17-oxysteroids in the blood and gonadotropins in the urine reported in this paper.

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TREATMENT OF CARDIOVASCULAR EMERGENCIES*

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Cardiovascular emergencies are extremely important to the physician because there is no time to go home and read before performing the therapy; something has to be done fast and it had better be right.

There are five main groups of emergencies: disturbances of the cardiac rate and rhythm; attacks of respiratory embarrassment; coronary episodes; vascular episodes; and cerebrovascular accidents. In addition, you should keep in mind that one does not exclude the other; in particular, a coronary attack may be followed by respiratory embarrassment, vascular collapse, or disturbances of the rhythm.

Disturbances of Cardiac Rate and Rhythm

The *disturbances of the cardiac rate and rhythm* may be summarized as: supraventicular tachycardia, ventricular tachycardia, atrial flutter and fibrillation, and Stokes-Adams attacks.

In cases of *supraventricular tachycardia,* the most important emergency treatment is *to stimulate the vagus nerve.* Reflex vagal stimulation can be done by massaging the carotid sinus area, one side at a time, or by compressing the eyeballs. I must say that I always found the last maneuver more effective. There are many other maneuvers which the patient usually tries himself before going to the doctor, like swallowing a big bolus of bread or sticking his fingers in the throat.

If these maneuvers have been tried and failed, the physician has to try drug therapy, best being *intravenous digitalization.* In these cases, one does not use regular digitalization. It has to be a large dose and a rapidly-acting drug, which is why cedilanid or digoxin should be preferred. Usually 4 cc. of cedilanid i.v. are tried and often the patient experiences the end of the attack within a half-hour. In cases where digitalization is ineffective, one can try to repeat the reflex stimulation half an hour after the intravenous injection. Sometimes, even when the drug fails to act, subsequent stimulation of the vagus is effective.

Another drug which can be tried is *prostigmine bromide,* in doses of 15 to 45 mg., several times a day by mouth. Injections of prostigmine can be given, but they are more delicate to handle.

In a case of *ventricular tachycardia,* different drugs should be used. Reflex stimulation is not useful and might even be dangerous. In ventricular tachycardia, one has to find out if there is any toxic element involved, like excessive digitalization. In such case, the drug should be withdrawn.

Two drugs can be used, quinidine and pronestyl. Pronestyl seems to be slightly more effective than quinidine. The dosage for *quinidine* is 0.2 to 0.6 gm. every three hours, starting with 0.2 and then increasing later on in subsequent stages until the attack is arrested. The dose of *pronestyl* (procaine amide) is about 0.8 gm., again every three to four hours.

The effect of these drugs disappears withing 2 to 4 hours; therefore, they should be given at frequent intervals, day and night.

In a case of *atrial flutter,* the conventional therapy is that of trying to transform the episode into one of fibrillation, because, in atrial flutter, the ventricles may start beating so fast as to lead to heart failure, while in fibrillation this does not happen. Transformation of flutter to fibrillation is done by means of a toxic dose of *digitalis.* One can start with an i.v. injection of 4 to 6 cc. of cedilanid, and, at the same time, start oral administration of the same drug, so that, within 24 hours, the patient has received a large amount of digitalis. This may cause vomiting, but, in these cases, I would not mind that.

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After onset of fibrillation, one can do one of two things: If the patient has any evidence of failure, one should continue the digitalization with a maintenance dose; if the patient has no failure, the best is to use *quinidine* and to discontinue digitalis.

If flutter does not change into fibrillation or sinus rhythm with digitalis, one can try quinidine. If this is also ineffective, then the only thing to do is to keep the patient at rest. In certain cases, normal rhythm can return spontaneously, without any further therapy.

In the case of *paroxysmal atrial (auricular) fibrillation,* I have found that the most useful therapy is to give an injection of *morphine plus atropine.* If there was a coronary episode, *oxygen* should also be administered.

If the patient is receiving digitalis, then you have to consider whether digitalis is absolutely necessary, because digitalis, by stimulating the vagus, may somewhat favor the auricular fibrillation.

The *Stokes-Adams attacks* are usually caused by a-v block. One drug which seems very useful is i.v. *isuprel.* In a case of slow ventricular rate or cardiac arrest, isuprel is given in a dose of 0.02 mg. It is a minimal dose but one which is effective in stimulating the excitability of the ventricles and the conduction of the a-v bundle, and therefore may re-establish a normal beat.

A few patients benefit from an intravenous injection of *aminophyllin.* These are cases with severe coronary heart disease, where impairment of the coronary circulation is responsible for the a-v block.

I would like to mention a very important device, *the electric pacemaker,* which is now becoming more and more in use and which should be present in every hospital.

The "pacemaker" records automatically the heartbeat of the patient through an electrocardiogram, and does not act as long as the heart of the patient beats. If the heart stops or slows down beyond a certain limit (like 10 or 5 per minute), the electric pacemaker automatically takes over and sends impulses through the chest wall to the heart, and keeps the heart beating at the rate set by the physician.

In a case of *ventricular fibrillation, flutter,* or *standstill,* therapy is different In the cases of ventricular fibrillation, this disturbance is revealed by the electrocardiograph, and you can hear a faint buzzing sound through the chest wall indicating that the heart is still contracting. The first thing to do is to inject *procaine* intracardially, then to use an electric defibrillator, which sends an electric shock to the heart and arrests the fibrillatory contractions.

After this, the heart beat should be re-established. This can be done in two ways: One is by means of drugs—namely by injecting either a mixture of epinephrine and procaine, or isuprel in dose of 0.02 to 0.04 mg., directly into the left ventricle.

The other is to use the "electric pacemaker" sending adequate electric impulses through the chest wall to the heart and keeping the heart beating. In other words, with ventricular fibrillation, you have the first phase, in which you stop the fibrillation and arrest the heart; and the second phase, in which you stimulate the heart and start its beat again.

The electric pacemaker has a double purpose and can be used for defibrillation as well as for stimulation.

Attacks of Respiratory Embarrassment

The *attacks of respiratory embarassment* can be listed as follows: paroxysmal nocturnal dyspnea, paroxysmal pulmonary edema, bronchial asthma, Cheyne-Stokes respiration, and pulmonary embolism.

Pulmonary edema differs from paroxysmal dypsnea because, in the former, there are a lot of rales in the chest and fluid pours from the capillaries into the alveoli and the bronchi while, in the latter, the patient's lungs and bronchi are dry. In paroxysmal dypsnea, there may be dry, wheezing noises, but there is no fluid, and the patient's condition somewhat resembles that of bronchial asthma.

In *paroxysmal dyspnea,* an injection of 10 to 15 mg. of *morphine* is usually adequate; the drug can be given subcu-

taneously because there is no extreme urgency. One should remember that morphine is dangerous in bronchial asthma; on the other hand, epinephrine, which is useful in bronchial asthma, is detrimental in paroxysmal dyspnea of cardiac origin. This is why, in the few cases where diagnosis is difficult, one can avoid both morphine and epinephrine and use i.v. *aminophyllin* until the diagnosis becomes clear.

In *pulmonary edema,* there are two main groups of cases: those with high blood pressure and those with normal or low blood pressure. Patients of the second group should be treated in a different way from those of the first.

In the first group, the one with the high blood pressure, all the classic accepted therapies can be used: venesection, application of tourniquets, morphine, i.v. mercurial diuretics, i.v. digitalis. All these procedures or drugs have one effect: they decrease the venous return to the heart. This is why these procedures, which are good in hypertensive patients with pulmonary edema, may be detrimental in those with low blood pressure or where the blood pressure has a downward course.

The same applies to other, more recently described, drugs and procedures. Among the drugs, *arfonad,* which is a sympatholytic drug, has been used with great success; it causes complete sympathetic paralysis, dilatation of the peripheral vessels, and improvement of pulmonary edema; but again, it would be dangerous in patients with a tendency toward shock. The other is *pressure respiration.* Pressure respiration with the mask and the expiratory valve increases intrathoracic pressure and, by so doing, compresses the venae cavae and decreases venous return. Therefore it is useful in the first group, detrimental in the second.

That is why, whenever a patient has a tendency towards shock, or a blood pressure which is below 100 (whether it is a coronary or a mitral patient) one should be very careful in the selection of drugs or procedures. One might still give a small does of morphine (5 to 10 mg.). One should give oxygen without pressure valve or mask. One should use that procedure which was described by our group four years ago; namely, *alcohol vapor inhalation with oxygen.* This is a purely symptomatic method of treatment but may interrupt a vicious circle. It acts in a physico-chemical way on the foam, it reduces the volume of the latter to a small amount of fluid which can be easily expectorated, and permits the oxygen to penetrate to the alveoli and improve respiration.

The *Cheyne-Stokes respiration* requires a symptomatic treatment.

First, i.v. *aminophyllin* can be given. This dilates the vessels of the spinal cord and the medulla and at the same time stimulates the respiratory center. Then venesection can be resorted to if the patient has either high blood pressure or heart failure and high venous pressure. A glucose infusion by the drip method is also sometimes advisable.

Bronchial asthma is not a cardiac emergency. However, one should remember that, when an attack of bronchial asthma occurs in a coronary patient or in a patient with evidence of right ventricular embarrassment, it might lead to frank heart failure. In these cases, like in those with cor pulmonale, morphine in contraindicated.

If the patient needs sedation, this can be administered, but at the same time, the patient should be placed under the action of an *artificial respirator.* When the chest is rhythmically ventilated and oxygen can be given without the bad effect of depressing the respiratory center, then one can use any drug and the oxygen itself will be extremely useful. Oxygen or sedatives, without the respirator, would slow down the respiration, increase the effect of the disturbance, and even lead to more serious cardiac and respiratory failure even causing death.

In a case of *pulmonary embolism,* we are still groping in the dark, because the few accepted methods of treatment are not always successful.

As you know, *morphine and atropine,* or *demerol,* which also has an atropine-like effect, are useful in these cases. Oxygen is given as a matter of fact and helps. Digitalization may be used in some cases in which there is serious dilatation of the right heart. The prob-

lem of *papaverine* has been raised. Papaverine is a vasodilator and can be given unless the blood pressure is going down rapidly. If the blood pressure is still high or normal, then papaverine may be useful by dilating the branches of the pulmonary vessels and possibly allowing the embolus to move further into a smaller branch.

On the other hand, if the pressure is low, papaverine would further decrease it and might cause coronary insufficiency and a myocardial infarct. Therefore, papaverine would be contraindicated in those cases. As a matter of fact, if the blood pressure drops too rapidly or too low, *levofed* might be given by the intravenous drip method in order to sustain it, thus allowing for a better supply of blood to the coronary vessels.

Coronary Episodes

The *coronary episodes* may be summarized as episodes of angina pectoris (or cardiac pain), and the frank coronary occlusion causing a myocardial infarct.

In *angina pectoris,* symptomatic therapy is based on the old accepted method of giving a tablet of *nitroglycerin* under the tongue. I would like to mention that too large doses at one time may be detrimental. This applies also to amyl nitrite, which I frankly do not advocate.

We have proven in our laboratory that an ampule of amyl nitrite may be followed by the ECG evidence of serious coronary insufficiency. This is because the severe drop in blood pressure decreases the amount of blood going through the coronaries. Clinical studies have shown that large doses of nitroglycerin can have the same detrimental effect.

In the case of a *coronary occlusion,* I can only list bedrest, oxygen, morphine and atropine, and the use of phenobarbital. I would like to remind you that drugs like morphine and phenobarbital should be used not only against severe pain and for a brief time, but for several days and in all cases of occlusion. The reason is, that in these cases, detrimental reflexes contribute to the vascular collapse and favor many other dangerous phenomena, including arrhythmias. By blocking the central nervous system, you can obtain a better level of blood pressure and avoid those reflexes which might be responsible for arrhythmias or paroxysmal tachycardia, and indirectly lead to heart failure.

There are two complications which I have to briefly mention: One is *shock,* where we have to resort to the accepted methods of therapy. From the various procedures which have been advocated, the only one which seems effective is to start *as early as possible* and give *fluid with levofed intravenously,* and the only precaution I would use is to give it more slowly than in the average patient with shock. The reason is that, if you give it too rapidly, the patient may fall into pulmonary edema or present acute dilatation of the right heart. If the patient has both pulmonary edema and shock, the only thing to do is to give fluid even more slowly, under the supervision of the doctor.

In order to prevent worsening of pulmonary edema, the patient should also receive alcohol vapor with oxygen, starting at the same time as the intravenous levofed. The alcohol will prevent the patient from suffocating in his own fluid, while at the same time one tries to raise the blood pressure to a tolerable level.

Vascular Attacks

In regard to the *vascular conditions,* they can be summarized as two. *Shock* was already mentioned. In a case of shock, keep the patients warm, reassure them, and give morphine, though with care. Oxygen is useful, but remember that an oxygen tent sometimes cools the patient too much. If the patient is chilled, you can give oxygen by nasal catheter or by mask, and warm him with hot water bags and blankets.

In regard to the *vascular collapse,* you have to remember the various possibilities. One is the vasovagal attack; one is the vascular collapse of an infection; and others are vascular episodes due to psychogenic impulses, like, for instance, the sight of something repellent or fearful.

In these cases, horizontal, or even better, head-down position is indicated. If you have a couch, put the patient on the couch with the head down. Another useful maneuver is compression of the ab-

dominal aorta, which is very successful. Just push with all your strength at the level of the umbilicus. If the patient is too fat, raise the legs of the patient at a square angle and let the blood from the lower extremities flow toward the heart. This is also successful. Another possibility is that of slapping as violently as possible your patient. It is a very good way of reawakening your patient. If the patient is in a twilight condition, he will get mad by your slugging and this will cause secretion of epinephrine, which is useful. If the collapse continues you can give atropine and epinephrine. Atropine will block the vagus nerve and prevent slowing of the heart; epinephrine will give vaso-constriction of the periphery and increase blood pressure.

If you don't want to use these drugs, you can give *metrazol* which stimulates both the vasomotor and the respiratory centers; it can be given either subcutaneously or intramuscularly.

Cerebrovascular Accidents

The *cerebrovascular episodes* or *accidents* are classically three: hemorrhage, thrombosis, and embolism. And classically there are three kinds of therapy. Serious doubts have been raised as to the difference between cerebrovascular hemorrhage and cerebrovascular thrombosis. It has been stated that the former leads to passing of red cells through the capillary walls into the area of infarction, so that at postmortem they might find a big clot of blood there and therefore diagnose a hemorrhage. And if there is a hemorrhage, that might even compress the surrounding vessels and lead to effects similar to those of thrombosis. At the present time, and considering the frequent difficulty in diagnosing correctly whether it is a thrombosis or a hemorrhage, it would be better to have a single type of therapy for both.

Embolism is usually well recognized because frequently one can find a cause for it. Usually a bacterial endocarditis or a mitral stenosis with fibrillation, or a myocardial infarct.

If the patient's blood pressure is high (at least above 150) you can proceed to a venesection, with the bloodletting of not more than 300 to 500 cc. If the patient's pressure is normal or lower, such a maneuver should be avoided. Infiltration of first cervical ganglion has been advocated, especially for thrombosis, but the results are controversial. If done at all, it should be done within the first 12 hours.

Lumbar puncture is frequently useful by decreasing the increased pressure of the spinal fluid. Injections of either 100 cc. of 33% hypertonic glucose or 20 cc. of 10% magnesium sulfate can be done. The purpose of these hypertonic solutions is to attract fluid from the brain tissues into the blood stream and thereby decrease edema of the brain.

This edema frequently spreads to a much larger area than that of occlusion and therefore makes more serious the effects of the attack. If the patient has convulsive motion, you can give sedatives, phenobarbital or chloral hydrate. If there are no convulsions, sedatives should be avoided. If the patient has an attack of pulmonary edema, then again the best way is to use alcohol vapor with oxygen.

The use of anticoagulants, especially heparin, has been advocated both in cases of embolism and in cases of thrombosis. In these cases, the use of these drugs is still controversial.

In regard to vasodilators, like papaverine and aminophyllin, these are to be used only in hypertensive patients, and in those cases where you can practically exclude a cerebral hemorrhage; otherwise they might be detrimental.

One procedure which seems useful is 20-30 minutes of oxygen inhalation with 3% carbon dioxide. This leads to vasodilation of the cerebral vessels.

CLINICOPATHOLOGIC CONFERENCE

Presented at Mount Sinai Hospital, Chicago, Illinois

DR. L. FELDMAN, Chairman **DR. H. RAPPAPORT, Secretary**

CLINICAL HISTORY

1st Admission: (February 16, 1956-March 10, 1956).

This six year old Negro female entered Mount Sinai Hospital for the first time on February 16, 1956, because of a cough and elevation of temperature of one days' duration and suspected congestive heart failure.

History obtained from the mother indicated no knowledge of any type of heart disease until the age of 2½ when the child had a cold, was seen at another hospital, and had a heart murmur elicited. The patient was not hospitalized at that time. An ECG and a chest x-ray were done, and the mother was told not to worry at that time. She had no knowledg of cardiac catheterization or angiography having been performed. The child had a history of recurrent colds and sore throat. Recent onset of dyspnea two weeks prior to admission with unusual vomiting occurred, and her heart was beating faster. No ankle edema was ever noticed, nor was there any history of rheumatic fever.

Past History: The child was a bottle fed infant. She sat up at the age of one month; stood at nine months; talked sentences at 18 months, but did not walk until the age of two years. The child gained weight normally, but at the age of 5 years she began to fail to gain. She had always been an active child, never having been "blue," not even when crying. She had scarlet fever in November of 1955.

Physical Examination: Examination on admission revealed a 6 year old, thin, poorly developed, malnourished colored female in acute respiratory distress. Dyspnea but no cyanosis was present. Pulse was 140 and regular; blood pressure was 102/60; respiration 36; temperature 103°F. The skin was warm and moist. The conjunctivae were pale; the funduscopic examination revealed pale retinas, but otherwise normal eyes. The ears were negative. The tongue was dry with prominent papillae. The chest was of asthenic build. Dullness and crepitant rales were elicited in the right apex. The heart was enlarged with a boot configuration and an apex beat in the 6th intercostal space 8.0 cm. to the left from the mid-sternal line. There was a rough grade IV systolic murmur all over the precordium with maximum intensity near the apex. A questionable mid-diastolic murmur in the apical region was elicited. P_2 was very loud and split. The abdomen was flat and soft; non-tender, and no masses were palpable. The extremities were thin and poorly developed. Tendon reflexes were hypoactive, and the fingers were hyperextensible.

Hospital Course & Treatment: The patient was placed on antibiotics (Penicillin and Achromycin) and was digitalized with Digitoxin. She received 0.1mg. daily from the beginning. A rapid digitalization was performed on March 3rd with 0.1mg. of Digitoxin q. 6 hrs.; (4 doses) and she was maintained later on 0.05mg. of Digitoxin daily. Extensive cardiology work-up was performed including angiocardiography and cardiac catheterization. The patient improved on the treatment and was discharged from the hospital on March 10, 1956.

Laboratory Data—1st Adm.

Cardiology work-up: 2/20/56: showed a systolic irregular murmur over the entire precordium, loudest at the apex and pulmonic areas, and a loud prolonged second pulmonic sound. This type of diastolic murmur is that frequently observed in relative mitral or tricuspid stenosis (in congenital or rheumatic hearts).

Cardiac Catheterization—2/28/56: showed no evidence of significant left to right shunt between the chambers. A small left to right shunt between the atria could not be ruled out.

ECG—2/29/56: reported as borderline tracing, non-specific.

Angiocardiography — 3/10/56: showed an enlarged left atrium and some delay

in the emptying of the left atrium and ventricle.

Chest x-ray—2/16/56: showed a very large, bulging heart with considerable enlargement of the right ventricle and a relatively small vascular pedicle. The right lung vessels were increased. The left lung was hidden behind the heart shadow and was not well made out; there may be a large ventricular or auricular septal defect.

Blood count (admission): RBC-4.87 mil; Hgb. 10.9; C.I. 0.72; WBC 4,800; Segs-44; Eos-6; Lymphs-48; Monos-2; Platelets-adequate; 1+ anisocytosis.

3/9/56: RBC 3.9 mil; Hgb. 10.9; C.I. 0.89; WBC-5,750; Platelets-adequate; Stabs-9; Segs-70; Eos-1; Lymphs-18; Monos-2.

Blood culture: No growth.

2/28/56: Antistreptolysis titer — 125 Todd units.

2/25/56: "C" reactive proteins-4+.

2/17/56: Throat culture: Negative for Beta Hemolytic Streptococci.

* * *

2nd Admission: The patient was readmitted to Mount Sinai Hospital on March 26, 1956, because of breathing difficulties, cough, and elevation of temperature.

Physical Examination: The positive findings on admission were: A poorly nourished Negro female with rapid, shallow respirations. Pulse 140; Respiration 45; Blood pressure 100/60. The tonsils were red and hypertrophied with pus in the crypts. The pharynx was injected. The chest was hyperresonant throughout with sibilant rales in both bases. The expiratory phase was prolonged. There were no changes in the cardiac findings from the first admission. The patient improved on antibiotic therapy. She also received 0.05mg. Digitoxin daily and was discharged on April 2, 1956.

Laboratory Data—2nd Admission

Blood count: RBC-4.13Mil. Hgb. 10.6; C.I. 0.83; WBC 8,600; Stabs-3; Segs-80; Lymphs-14; Monos-2; Platelets-adequate.

Anisocytosis-1-2+; Poikilocytosis-2+; Throat culture (3/27) Negative for Beta hemolytic Streptococci.

Urinalysis: Acetone-moderate; WBC 2-3; Blood culture (3/27) no growth.

3rd Admission: (April 26-22, 1956).

Readmission of the patient was required because of possible congestive failure. She had been on Digitoxin, 0.05 mg. daily. She developed nausea and vomiting, and the doses were decreased to 0.025 mg. daily. The findings on admission were a grade IV systolic murmur at the 3rd left intercostal space. The lungs were clear. No abdominal masses were palpated.

Clinical Course: The Digitoxin was discontinued because of nausea and vomiting.

Laboratory Data (Third Admission)

Blood count: RBC-4.38 mil; Hgb. 10.9; C.I. 0.70; WBC-3,800; Stabs-1; Segs-50; Monos-2; Lymphs-43; Monos-4; Platelets-adequate.

Poikilocytosis-1+; Hypochromia-1+; nucleated RBC-1; Blood cultures—no growth.

Urinalysis: 4/17: pH-5.5; Sp. Gr. 1.030; Protein-3+; RBC 1-6; WBC-few; few mucus threads; few bacteria.

* * *

4th (FINAL) Admission: The patient was re-admitted to Mount Sinai Hospital on April 28, 1956, because of dyspnea and orthopnea.

Physical Examination on admission revealed a blood pressure of 105/60; pulse of 160; respiration of 40 and temeperature—normal. The chest had no dullness. Rales in the right base and harsh breath sounds in the left base were elicited. The patient was dyspneic and orthopneic. No generalized edema was present.

Hospital Course: The patient was immediately placed in an oxygen tent and 4.5mg. of Digitoxin I.M. stat and 0.2mg. orally were given. She received also 1/16 gr. of M.S. and Mercurhydrin 0.5cc. The patient did not improve; she stopped breathing while the nurse was changing the linens due to incontinent urination and was pronounced dead at 9:40 P.M. on April 28, 1956.

Added post-mortem note: The mother stated that the patient experienced several episodes of chest pain associated with back aches. The same thing occurred shortly preterminally.

Laboratory data—4th Admission

Blood count: RBC-4.59 mil; Hgb. 11.7; C.I. 0.82; WBC 8,500; Stabs-2; Segs-71; Lymphs-19; Monos-8; Platelets-adequate.

Anisocytosis-1+; Poikilocytosis-3+.

Nucleated RBC-5/100 WBC. Polychromatophilia-1+.

* * *

Discussion by Dr. Howard Weiss*

Before discussing the differential diagnosis, I would like to summarize the essential history and findings in this case. This is a six-year old Negro female, with history of a heart murmur that was known since at least 2½ years of age; therefore, probably a congenital murmur. She was a very tall (Height 49½ inches) and thin (Weight 42 lbs.) child, poorly nourished with markedly relaxed joints, disproportionately long extremities, and spider fingers. She had a very large heart, which was generally enlarged, and had a systolic and diastolic murmur at the apex. The electrocardiogram showed left ventricular hypertrophy. Cardiac catheterization was inconclusive. Angiocardiagraphy revealed an enlarged left atrium with delayed emptying of both the left atrium and left ventricle. The patient suffered with repeated episodes of bronchopneumonia and congestive heart failure.

I would now like to discuss the pertinent features of this case as follows:

(1) Is the pathology on a congenital or acquired basis? I feel that the young age of the patient when the murmur was first heard, the fact that at age six she had such marked cardiac enlargement, along with the physical characteristics of arachnodactyly, all point more to a congenital basis for the cardiac pathology, rather than acquired.

(2) What pathology could cause such marked cardiac enlargement with repeated episodes of congestive failure at this relatively young age without a shunt being present? If the cardiac pathology is on a congenital basis endocardial fibroelastosis would be a good possibility; although survival rates to this age are very low in this condition. In the group of acquired heart diseases, rheumatic heart disease or chronic myocarditis would be possibilities.

(3) In considering the mitral systolic and diastolic murmurs, in the congenital group fibro-elastosis again is a good possibility, since the mitral valve is commonly thickened and deformed in this condition. Congenital mitral stenosis could also be considered, but is extremely rare. In the acquired group, rheumatic heart disease would again be a possibility. Clinically, one would have to rule out a congenital malformation with a left to right shunt such as an interatrial or interventricular septal defect. However, the catheterization showed no significant shunt.

(5) What could cause repeated episodes of congestive failure in a six-year-old child? Rheumatic heart disease would be a very unlikely possibility at so young an age. Therefore, a congenital malformation is much more likely, such as the group of "idiopathic" cardiac hypertrophy, the most common of which is endocardial fibro-elastosis.

From this analysis of the features of this case, I would form my impression as follows. My total diagnosis is Marfan's syndrome; i.e., arachnodactyly, congenital malformation of the heart, high-arched palate, subluxation of the lens of the eye. This child had the typical features or arachnodactyly — unusual height for her age group, markedly asthenic stature, poorly developed musculature, hyperextentensible joints, "spider" fingers. Funduscopy did not reveal any abnormality of the lenses. However, I do not feel that this would rule against the diagnosis. As to the specific diagnosis of the cardiac lesion, I believe, as I said, that this patient probably had a congenital cardiac defect. The most common cardiac defects accompanying Marfan's syndrome are the septal defects. However, the murmurs in this case were not at all typical of either **IA** or **IV** septal defects, and the cardiac catheterization showed no evidnce of a shunt. My first choice, therefore in the cardiac diagnosis is endocardial fibro-elastosis.

In support of this diagnosis are the following: absence of cyanosis or club-

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bing, early history of murmur, marked generalized cardiac enlargement, repeated episodes of left heart failure, electrocardiogram showing left verticular hypertrophy, and the systolic-diastolic mitral murmurs which may be seen in this condition. The only serious point against the diagnosis of endocardial fibro-elastosis is the age of the patient. Death in this condition usually occurs within the first year of life. It is rather unusual that a child with this condition reach the age of six. However, patients with this condition have been known to live even longer, the oldest on record living to the age of 27. Therefore, the age factor does not seriously rule against the diagnosis of endocardial fibro-elastosis in this case. As for other possibilities in the cardiac diagnosis, I feel that we still must rule out rheumatic fever early in life followed by repeated episodes of carditis with development of mitral insufficiency and stenosis leading to cardiomegaly and repeated episodes of congestive heart failure. However, this clinical picture of rheumatic heart disease would be extremely unusual at six years of age. Therefore, I will stick to my first diagnosis of edocardial fibra-elastosis as part of Marfan's syndrome.

Discussion by Dr. Henry Grinvalsky**

Before I discuss the anatomical findings in this case I should like to tell you about several interesting features which I had learned from the mother of this patient. She was kind enough to drop into my office for an interview, and she brought along two photographs of the child. They proved rather interesting. The first photograph was taken when the child was a little over 5 years, and you can see that there was a long, tapering head. You will also notice that the ears were rather prominent. Unfortunately the tops of the ears were hidden by hair, but the mother volunteered the information that they were oddly pointed. The long and tapering head (dolichocephaly) and prominent and pointed ears have been observed quite frequently

FIGURE 1

Left Ventricle—The endocardium of the intraventricular septum is markedly thickened especally beneath the aortic ring. The aorta is prominently dilated.

in association with arachnodactyly (Marfan's syndrome). This photograph also emphasizes the unusual long phalanges that the child had. This second photograph had been taken about 6 months later. In this one we see the child wearing a hat, but notice how peculiarly it sets on the dome leaving quite a bit of head uncovered. It seems to be perched on a peak. The mother said that hat buying for this child had always been a problem. None seemed to fit right. One other feature was also disclosed by the mother. The patient had an oddly shaped chest, and from her description it would best fit into the category of a mild "pigeon-breast." At the autopsy table, the arachnodactyly, aural changes, and dolichocephaly were verified.

The principal pathological alterations were found in the heart, aorta, and lungs. The heart was prominently enlarged and globular. The epicardium was not remarkable. The sectioned heart revealed dilatation of all chambers but

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principally the left ventricle and atrium. The left ventricular wall was markedly hypertrophied and measures up to 2.0 cm. in thickness. The right ventricular wall was moderately hypertrophied, and it measured up to 1.0 cm. in thickness. The heart weighed 200 grams which represents slightly more than a 2X increase in weight, considering the child's height and weight. There were no abnormal communications between the various chambers, and the coronary circulation was regular. The endocardium of the left atrium was opaque and thickened, and there was an ovoid, elevated, cushiony 4.5x3.5 cm. plaque on the anterior wall. It would not be difficult to mistake this plaque for a MacCallum patch if one were not impressed by the prominently elevated and wrinkled appearance and the cushiony texture. The mitral valve was thickened. The cusps were fused, and the chordae tendineae were thickened and shortened. But they were not the fibrous, scarred character of a rheumatic nature; instead, they had a somewhat edematous, cushiony character similar to the ovoid patch on the atrial wall. The mural endocardium of the left ventricle was very thick, more prominently on the septal surfaces especially beneath the aortic ring. The sinusoids leading into the myocardium were outlined rather boldly as the endocardial thickening lined their transected aspects, and they could be traced quite deeply into the left ventricular wall especially in the apical zone. The endocardial surfaces of the left side of the heart could be best described by the term "sugaricing," or better still, it seemed as if molten paraffin had been poured over the surfaces and allowed to solidify. The aortic ring was mildly dilated, but the leaflets of the aortic valve were only mildly thickened in rather uniform fashion. The aorta was moderately dilated in fusiform fashion, but evidence of an aneurysm was not detected. The major veins and arteries were normally distributed, of average diameters, and had regular gross appearances. Thrombi or emboli were absent.

The gross characteristics which you saw represented in the preceding slides might encourage an observer to interpret the changes as being the result of rheumatic disease if textures and consistencies were not taken into account. The histopathology showed alterations almost entirely restricted to the endocardial surfaces of the left side of the heart. When H. & E. preparations were studied, only an increase in the thickness of the subendothelial zone of the endocardium was evident. However, Verhoeff elastica and Masson stains demonstrated that the endocardium contained a marked increase of elastic fibers with a concomitant increase in collagen. The elastic fibers were coarse and elongated. This change extended down along the sinusoids extending along the myocardium. There was only minimal alteration of the myocardium proper except for some minute patches of fibrosis, but there was no evidence of active or old inflammatory disease. This alteration in the endocardium is rather characteristic of the

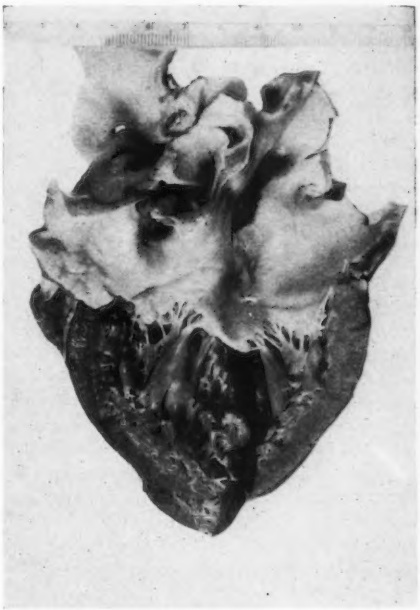

FIGURE 2

Left heart showing mitral valve and atrial wall alteration stimulating changes seen in rheumatic heart disease. Note the outlining of the myocardial sinuses by thickening of endocardium especially in apical region of left ventricle.

entity reported in the literature as endocardial fibro-elastosis, and since it is unassociated with congenital defects or a myocardial inflammatory disease, it is classified as being of the primary type. In degree it rivals any case thus far reported in the literature. The mital valve showed no evidence of scarring or vascularization as is seen in rheumatic disease. The thickening was due to an increase in elastic fibers concentrated especially on the auricular surface, and, in addition, there was a myxomatous appearance of the remaining stroma rendering to the tissues a somewhat embryonal appearance. This change has been described previously in cases of endocardial fibro-elastosis. Sections of the left atrial wall including the ovoid plaque revealed that embryonal looking fibro-myxomatous tissue had proliferated upon the endocardial surface. Spindle or spider-like cells were sparsely scattered by seas of pale staining, basophilic, granular material which gave a faint mucicarminophilia when the Mayer's mucicarmine stain had been used. The underlying subendocardial tissues, that is, the tissues in the lamella beneath the fibromyxomatous patch showed a prominent increase in coarse, elastic fibers and collagen.

Hematoxylin and Eosin preparations of the aorta revealed a fairly regular architecture excepting that there seemed to be a mild interstitial edema in the media. This suggested the possibility of early myxomatous degeneration which was verified by the presence of mucicarminophilic material in the interstices of the media when sections were stained according to the Mayer's technique for mucins. This point is noteworthy insofar as older patients with Marfan's syndrome may be found to have a dissecting aneurysm at post mortem, and death is not uncommonly due to rupture of such aortic aneurysms. These aneurysms result from myxomatous degeneration of the media. We did not find an aneurysm in this case, but if we had, it would have nicely accounted for the severe back pain experienced in the terminal episode. I fear we have no anatomical lesion to account for the patient's back pain.

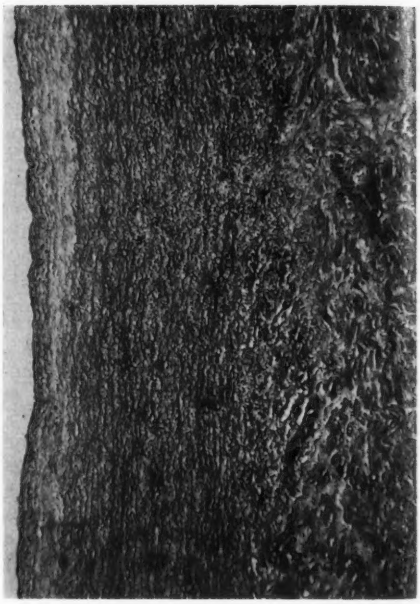

Figure 3.

Left ventricular wall, septal aspect, showing marked thickening of endocardium with prominent increase in elastic fibers. Verhoeff elastics stain 70x.

The lungs weighed 280 grams and 150 grams right and left, respectively. The pleural surfaces were smooth, glistening, and without evidence of adhesions. The left lung had two regular lobes. The right lung, however, showed no distinct lobation. There was no middle lobe. An incomplete fissure incompletely divided the lung into two lobes. Viewing the hilar aspects, no fissures were at all evident. The right bronchus had only two major subdivisions, one to the superior lobe and one to the inferior lobe. The vasculature also conformed to this pattern. Abnormal lobation of lung has been reported in Marfan's syndrome. In addition to this abnormal lobation, the lungs were voluminous, firm, and relatively airless, and their surfaces had a dusky appearance. The sectioned surface became bathed in copious amounts of fluid blood. There was a uniform increase in consistency without focal consolidation, and decreased crepitus was

also rather uniform. After fixation in formalin, the surface of the lung assumed the rust-like discoloration so characteristic of chronic passive congestion. Sections confirmed the presence of advanced chronic passive congestion. In the larger septa, vessels with thickened walls were conspicous. The alveolar walls were thickened, fibrous, and contained numerous engorged capillaries. The alveolar sacs were loaded with mononuclear cells representing swollen lining cells or macrophages laden with hemosiderin. There was no evidence of an inflammatory exudate to indicate active or past inflammatory disease. Elastica preparations failed to disclose a notable increase in elastic tissue, and there was no evidence of pulmonary siderosis as has been recently described in association with advanced mitral disease. The hilar lymph nodes were not notably enlarged.

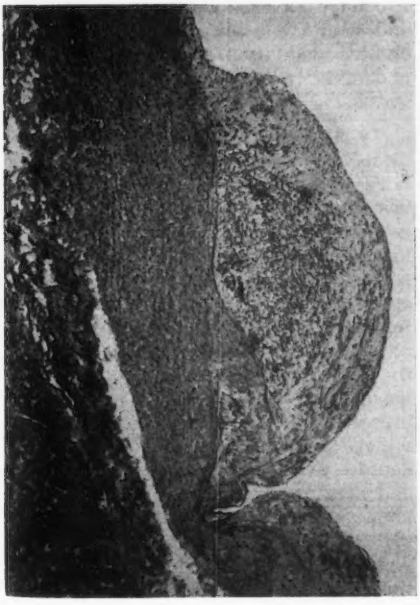

Figure 4.

Left atrial wall showing mound-like proliferation of spindle cells in a myxomatous matrix. The underlying endocardial lamella is markedly thickened. H & E 30x.

The liver had a regular size and shape, and its capsule was thin and smooth. The weight was 600 grams reaching the upper limits or normal for this age. The sectioned surface was bloody, and the lobular pattern was accentuated by tawny haloes conspicuously surrounding dilated central veins. The microscopic picture was one of severely engorged sinusoids leading from distended central veins with compression of hepatic cells in the central zone. Patches of hepatocellular necrosis were scattered throughout the central zones of the lobules. This change is related to the marked hypoxia the patient suffered during the terminal episode of congestive failure. Acute passive congesion was also reflected in the other viscera which were otherwise not remarkable.

The final anatomical diagnoses are summarized as follows:

1. ARACHNODACTYLY associated with:
   a. Dolichocophaly
   b. Aural changes
   c. Hyperextensibility of joints (clinical)
   d. "Pigeon-breast" deformity of chest
   e. Abnormal lobation of right lung
   f. Fusiform dilatation of aorta with early myxomatous degeneration
   g. ENDOCARDIAL FIBRO-ELASTOSIS
2. Mitral insufficiency
3. Cardiac dilatation and hypertrophy, left and right
4. Acute and chronic passive congestion of lungs and viscera
5. Pulmonary edema
6. Focal necrosis, liver

Several features of this case make further discussion of the anatomical findings imperative insofar as they relate to the arachnodactyly on the one hand and endocardial fibro-elastosis on the other. Thus far I have not encountered a reference to endocardial fibro-elastosis occurring in association with arachnodactyly. The following table summarizes

the most common cardiovascular lesions associated with the syndrome as reported by Marvel and Genovese in 28 autopsy cases collected from the literature since the original description in 1896 by Marfan:

Heart Lesions in Marfan's Syndrome (28 cases)

Interauricular septal defect	6	(21%)
Aortic stenosis	1	(3.5%)
Patent ductus arteriosus	1	(3.5%)
Rheumatic valvular lesions or endocarditis	10	(35%)
Valvular lesions of undetermined etiology	6	(21%)
Aortic aneurysm	16	(54%)

As you see, there appears to be an unusually high incidence of rheumatic valvular lesions and/or endocarditis. This appears to be a rather unusual association, and therefore, the cases which in their aggregate would imply this association deserve close scrutiny. In reading over the case reports, it readily became obvious that there was rather poor substantiation of the presence of rheumatic disease. Clinical evidence of rheumatic fever was not even suggestive in these cases, and most diagnoses were based upon gross appearances of the valves and mural endocardium. In other words, if there was thickening of the mitral valve, shortening and thickening of the chordae tendineae, and perhaps some thickening of the aortic cusps or suggestion of the presence of a MacCallum patch in the left atrial wall, the lesions were automatically attributed to rheumatic heart disease. At this point I want you to recall the gross description I gave in the beginning of this presentation. If we had not been critical, we too might have erred by attributing our valvular and mural aliterations to rheumatic heart disease. I should like to propose that a significant number of the cases of heart lesions found in association with arachnodactyly are not due to rheumatic disease but are in reality part of the basic mesodermal congenital defect and due to endocadial fibro-elastosis. Perhaps all of the cases reported as rheumatic disease in this syndrome fall into this category. This would eliminate the unusual incidence of rheumatic heart disease and arachnodactyly and thereby eliminate a problematic and puzzling association between two apparently unrelated entities. In addition, the valvular lesions of undetermined origin seen in association with arachnodactyly may also be valvular deformities resulting from endocardial fibro-elastosis which may not have been appreciated at post mortem. Hence, if we combine the rheumatic group and the valvular lesions of unknown origin and attribute them to endocardial fibro-elastosis where they properly belong if the significance of our case is properly accessed, we would find that endocardial fibro-elastosis would be associated with arachnodactyly in approximately 56% of the autopsied cases. I believe that this proposal has merit and would encourage a more thorough clinical evaluation of the cases of arachnodactyly with regard to the cardiac status.

My final words deal with the congenital aspects of arachnodactyly (Marfan's syndrome). A familial incidence has long been appreciated. During my interview with our patient's mother I inquired about family background. The patient was the mother's first child. She denied that any member of her family for several generations had any peculiar physical characteristics. The father of the child, however, had a long, narrow head; big, pointed ears; was pigeon-breasted; had difficulty with his eyes for which he had to wear glasses; and he definitely had long narrow extremities and long fingers. Hence, we have arachnodactyly associated with other abnormalities (Marfan's syndrome) in father and daughter. Since this child was born, the mother had remarried and has had another child, and this second child is normal.

GOALS OF THERAPY

H. H. GARNER, M.D.* and ABRAHAM W. SIMON, Ph.D.**

An appropriate article with which to follow up the one on medical history taking published in the last issue of this Quarterly would be one dealing with the goals of medical therapy in general, and the goals of psychotherapy as a special form of medical therapy. The way in which we have drawn sharp distinctions not only in medical practice, but in our society in general between physiological and psychic factors requires a rather detailed discussion to establish the underlying unity of physiological and psychic processes in an holistic conception of medical practice.

The goals being pursued in psychotherapeutic work are usually less clear to the physician not specialty trained in psychiatry. Yet the interpersonal relationship in which doctor and patient are always involved is often a most significant factor in patient improvement even when only "physiological" medicine is being consciously practiced. In Hyman's "An Integrated Practice of Medicine" the goals of therapy are expressed as follows: "The diverse modalities of therapy range from herbs of witch doctors to pure synthetic products, from accurately measured pharmaceuticals to the no less potent instrumentalities of psychotherapy and correction of general hygiene. At times, the physician functions as an arm chair advisor but he may participate in the more active procedures of instrumentation, injection, aspiration, or physical therapy. More often, he prescribes or administers drugs or biologicals for symptomatic, preventive or corrective therapy."

Hyman further emphasizes the need for individualization in therapy: "The regimen is modified by the nature of the ailment, the patient's way of life and capability for understanding, the co-operation of relatives and friends, the accessibility of apparatus and the practitioner's technical training and experience."

One can say that therapeutic interventions other than those made for the purpose of prevention are conventionally thought of as being directed against disease. In the care of a sick individual the treatment of the person must be considered in his totality with the goals usually being (1) cure, (2) removal of pathological tissue (3) symptom relief (4) rehabilitation (5) avoidance of recurrence or exacerbation of illness (6) slowing or arresting the disease process. The above therapeutic goals must be considered in relation to the factors mentioned by Hyman as important for the individualization of treatment. One might, for instance, have as a goal the removal of pathologic tissue, such as an osteoma, but important consideration might have to be given to special individual factors such as sensitivity to anesthetics, or the patient's obsessive preoccupation with the danger of cancer, or a superstitious idea that the osteoma has been a special protector in magically warding off serious illness in other members of the family.

So far, the presentation reflects a primary orientation to disease or affliction which places a high value on change in structure. A total view would also include the focusing of attention on perception, sensation and function. Disturbances in such processes must open a consideration of psychotherapeutic goals for the individual who seeks help with psychophysiological disturbances or conflicts over adjustment to living. These may stem from (1) structural or physiological changes of an objective, primary nature, or (2) disturbances in psychological homeostasis which are dealt with symbolically by the patient through autonomic bodily sensations and changes producing pain, or (3) maladaptive responses producing inefficiency in interpersonal competence.

A discussion of goals should also appraise the problem of definition which

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confronts all therapists. What is "health" and what "illness" might be best put, in the holistic view of the individual so aptly described by Steiglitz, as one in which man is studied in toto. The interest of the physician ranges concurrently from bio-chemical, cellular, and organ system considerations to a study of man in his familial, socio-cultural, and even cosmic involvement. Kubie referred to the same problem in trying to establish the essential difference between health and disease. To him an inclusive characterization of illness requires more than a listing of symptoms and a diagnosis. It reaches back into the origins of the illness, to the variations in vulnerability or immunity of different individuals. It includes states of potential or subclinical illness, during which for years there may be no external or symptomatic manifestation of the disease. At the other end of the pole, it encompasses the secondary and tertiary sequelae of the illness for the patient, for his family and friends, for his social group, and the community. These include not only the specific, direct effects of the active process, but also the residual damages to the patient and his setting that may follow on the active phase of disease. Kubie, however, points out that this all inclusive concept of disease need to be integrated with a precise understanding of the specific nature of the current illness, to the extent that such specificity is possible.

Goals in therapy are more readily understood by those with a more physiological orientation if one considers them in relation to the conventional customarily accepted goals for the treatment of persons suffering from an acute organic illness. Less clear, as yet unstandardized and not generally accepted are comparable realistic goals for the treatment of patients with chronic degenerative disease. The latter are more comparable to the kind of personal suffering, disturbances in equilibrium and ineffectiveness in living for which people seek psychotherapeutic help. The goals need also to be seen in the total frame of reference within which the therapist operates. The psychiatrically oriented physician would emphasize not only conventional, organic and diagnostic considerations but also his holistic approach to the patient. Goals for psychotherapy would also be more completely acceptable if they can be seen as derived from these more general goals for the management of any sick person.

Goals for the treatment of any person seeking help from the physician may fall within one or more of the following categories: (1) to save from death or (2) to "cure." This goal is possible for certain infectious diseases or disturbances in which the restoration of tissue to a normal state of function is the aim. The comparable goal of "cure" through psychotherapeutic work will be described later.

3. The removal of pathological tissue with a minimal or insignificant alteration in physiology, may be necessary as part of a live saving, disease arresting, or restorative process. This goal is best illustrated by the surgical removal of a tumor. The presence of brain tumors in some patients with mental symptoms points up the importance of a valid etiologic and diagnostic estimate before undertaking treatment. Psychotherapeutic goals in such instances are secondary to the goal of removal of pathological tissue.

4. Symptomatic relief. Freeing the patient of disturbing symptoms without significant alteration of tissue pathology or underlying psychopathology is a most frequent goal in medical therapy. Relief from unpleasant, painful, physical and emotional distress may be the only realistic goal available. Psychotherapeutic effort is frequently directed at a similar type of help; namely, freedom from or alteration in the form of symptoms so that they are less painful, tension producing, without alteration of the underlying pathological process.

5. In recent years the goal of rehabilitation has been emphasized in the treatment of chronic deterioratic diseases. Therapy directed at rehabilitation emphasizes (a) adjustment to the disability by attitudes of acceptance, and an increased utilization of secondary resources which may restore or maintain function (b) progressive improvement in

the efficiency of these secondary resources, until ideally they compare favorably in effectiveness to the primary operation. Psychotherapeutic procedures may be needed to help the physically handicapped patient to achieve such goals. Psychotherapy of patients with disturbances in psychological equilibrium alone may also have a similar rehabilitation goal; namely, return to work, acquire or improve social relationships, and develop new resources of interest and activities which are relatively free of phobic restriction or conflictual material, as thru sublimations.

6. Avoiding the recurrence or exacerbation of an illness is often a major goal of therapy. In the treatment of illness whose recurrence or exacerbation is probable, and where complete cure is not possible, the control of stress and deprivation that may foster recurrence would be a major effort. In ulcerative colitis, peptic ulcer, and asthma, one would want to see a significant expenditure of therapeutic effort in periods of remission to forestall recurrence. It is suggested also that psychotherapeutic effort may maximize the effective functioning of the ego, desensitize the patient to typical, anxiety provoking situations and people, and by manipulating the external environment improve well being and reduce the frequency of exposure to noxious stress. Such activity helps prevent recurrence of neurotic, and even psychotic upheavals.

7. Slowing, and hopefully arresting, the ongoing course of a disease process may be attempted, particularly in the deteriorative diseases. In pernicious anemia, the use of "specifics" relieves symptoms and prevents or slows down progression. In the treatment of chronic mental disability a similar goal may also be envisioned. Certainly for permanently institutionalized chronic, psychotic patients in state hospitals, the avoidance of further regression may be the only reasonable goal. Psychotherapeutic effort may include a wide variety of techniques with activity on the part of the therapist directed at just that goal; namely, arresting the progression of the disability.

Consideration of Psychotherapeutic Goals: Conceptions of the goal for psychotherapy generally are often expressed in the same terms as the goals for psychoanalytic treatment. These have been verbalized along such lines as bringing about changes in the personality, achieving maturity and successful interpersonal relations, or removing resistance to the expression of the repressed. When Freud expressed the dictum: "where it was, there shall ego be;' he indicated a goal for therapy. One might reword this famous concept in such terms as: what the patient wants to do, he is successful in achieving as it is in line with his abilities and potentialities, and results in experiencing satisfaction and happiness.

Kubie expressed a similar concept when he stated: "A state of greater health is achieved whenever those areas of life that are dominated by inaccessibly unconscious forces are shrunk so that a larger area of life is dominated by conscious or preconscious forces which can come to awareness when necessary." There is room for considerable discussion about whether the goal for therapy need always be a state of greater health as determined by the dominance of conscious forces. Certainly there can be no argument about such a goal when "cure" is the aim of therapy.

Schilders, Alexander's, and Fromm Reichman's formulations have moved more definitely in the direction of the socio-cultural dimension in specifying the successful integration of personal feelings and social action as the goal of psychotherapy. Such concepts as growth, maturation, independence, self-realization, harmonious adjustment, and all-around development which they tend frequently to use in their expression of goal ideas are non-specific and lend themselves to rather subjective definition, heavily loaded by the value orientations of the patient, the therapist, and the reader. It is questionable also whether such concepts can be spelled out adequately in any but non-objective, value oriented, socio-cultural terms. The rarity with which the ideal goal of "cure" is realistically claimed as having been

achieved, notwithstanding the emphasis and high status it has in the literature, may also be related to limiting socio-cultural factors in the patient's situation. Among these may be the therapist's specifications as to what his goals in treatment should be. These are not free of the value orientations of the therapist who as a person is also "culture bound." There is beginning awareness that socio-cultural distortions in the communication process between patient and therapist may prevent the initiation of a relationship, or even interfere with its continuance once it has been initiated. Associations, and the communication process among peoples appear to be markedly affected by social class position, ethnic background, color, religious orientation, national origin, or minority status. On closer and more intimate study, we conclude that these appear also to be associated with striking variations in the conceptualization of what constitutes growth, the achievement of maturation, independence, self-realization, harmonious adjustment, or all-around development.

The existence in our society of a good deal of class, color, economic, etc. variation, stratification, and social conflict among individuals and groups makes for the generation of widespread, socially induces stress, deprivation, and maladaptive responses. Such differences interpose barriers in communication or precipitate culture conflict when the patient and therapist do not share enough socio-cultural values and traits to establish a common meeting ground on which their relationship may develop. Shaffer, Meyers, and Seward have marshalled an impressive array of evidence to illustrate that not only the goals of psychotherapy, but the very conception of symptom and illness, the selection of cases, the selection of the treatment of choice, and the content of the psychotherapy itself, needs to take into consideration the value orientations and the socio-cultural backgrounds of the doctor as well as the patient in addition to the illness of the one patient and the skill of his therapist. Seward cites four adult cases analytically treated by Dr. Judd Marmor in which the socio-cultural deviance was so intertwined with the personal conflicts of the patient as to require a thorough going understanding of all three dimensions: (1) socio-cultural (2) individual-conscious (3) individual-unconscious for the formulation and achievements of a satisfactory therapeutic goal. Pollak has done similarly for work with children, focussing on an appreciation of the socio-cultural configuration of an entire family group as the object of treatment in setting the goal of care for a particular child whose needs involved the family with a therapist. Differences in the value orientations of patient and therapist would make for misunderstanding and the setting of unrealistic goals.

The opportunities and limitations offered by reality, as well as the potentiality of the patient, need to be constantly seen as sources from which goals for therapy are to be derived. As Schilder phased it rather succinctly, "It is the important task of the physician to develop the patient's personality according to his capacities, endowments and characteristics. The physician will be better able to do so if he has the conviction that the other human being is an entity of his own and is valuable in so far as he is a different person." Essentially such a goal in therapy enables a patient to have a maximum degree of enjoyment and gratification in living, with a maximum degree of resources free for active achievement in life. The concept of "maturity" expressed so frequently as Fromm Reichman's therapeutic aim is one which can at best be achieved by only a few patients. A need for compromise, and an acceptance of goals pegged to the many realistic factors which hamper the patient and the therapist, require some retreat from an idea goal of "cure." At the initial interview, during the period of trial therapy, or at any point along the course of therapy a goal exclusively directed at "cure" is not likely to be realistic.

In summary, several potential goal posts can be envisioned for psychotherapeutic work:

(1) One aimed at a maximum degree of personality change, aspiring to achieve

the goal of "cure." The attainment of a state of maturation may be the ideal and ultimate therapeutic result, as mentioned by Fromm Reichman, but socio-cultural as well as personal limitations need to be respected.

(2) One aimed at achieving as much toward such a goal as is possible with the knowledge that it will in all likelihood be only approximated. Therapy "interminable," geared to the resources and strivings of the patient, and the capacity and willingness of the therapist, can sometimes take place.

(3) One aimed at re-establishing a recent state of equilibrium which has been seriously disturbed. The treatment relationship will enable the therapist more readily to correct or reorient certain miscomprehensions and misjudgments, and to foster an improved integration of mental and emotional functioning, as in the case of an acute confusional state, delirium, or marked perplexity. Further re-evaluation and the establishment of new goals may then be necessitated by patient improvement.

(4) Diminution of the patient's difficulties in adaptation through advice, guidance, education and environmental manipulation. This goal can be achieved only after having established a relationship in which the security needs of the patient are seen by him as being fulfilled. The patient becomes better able to function in a socially effective manner with a minimum of disabling symptoms because of the support he feels exists through his having parentified the therapist.

Evidence as to which of these four goals have been most closely approached by the patient can be noted by making certain types of observation. (a) The goal has not been achieved through some type of suppressive, domineering or inspirational kind of alteration. It has been gained through the development of increased insight or self understanding, sufficiently beneficial as to lead to changes in feelings and action: (b) The pattern of interpersonal relations and interaction has changed in that it has become more characteristic of an older person or adult rather than that of an infant, child, or youth. Symptoms characteristic of these earlier stages have been left behind. (c) The patient now sees and has evidence of himself as a person capable of eliciting, and of accepting dignified and respectful consideration from others. (d) The patient now sees and has evidence of himself as a person capable of loving and being loved. (e) The patient has undergone changes in beliefs, in attitudes, and in characteristic reactions to stimuli which in turn lead to more harmonious and more effective relationships with persons known in the past and in the present. These in turn lead to more successful future patterns of interpersonal associations.

Conclusion: It can be said at this point that goals in therapy when seen as being determined by an holistic view of the patient including bio-chemical and psycho-social factors must of necessity lead to therapeutic action with biological, psychological, and social goals in mind.

A doctor in projecting goals for a patient with an obstruction of the bowel due to an incarcerated hernia may have in mind (1) save the life of the patient and correct a defect in anatomical structure, (2) bring about changes in the patient which may include an understanding and correction of his need for denial of illness so that the rather serious nature of the ailment was not recognized until the condition became a threat to life, (3) bring about an improved attitude on the part of the patient and wife so they could consider the possibility of a hernia repair in a son who had an inguinal hernia.

The possibilities of a therapeutic goal in which the totality of the situation is considered can be repeated by example after example.

Appreciation of the limitations of the etiologic approach in which emphasis is on the finding of a specific cause for a specific disease as the ultimate in scientific achievement, is becoming more and more widespread. We feel that an understanding of goals in therapy as requiring a total approach in the therapeutic endeavor needs frequent re-affirmation.

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